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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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SECTION ON MICROBIOLOGY

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BULLETIN OF
THE NEW YORK ACADEMY
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AUGUST 1949

ALLERGY AND ANTIHISTAMINE THERAPY*

A Review

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and

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For the allergist, the advent of the histamine antagonist has two appeals; viz., it offers a very satisfactory means of alleviating certain allergic symptoms, and it may throw light on the fundamental mechanism of allergy. Ever since Dale and Laidlaw[1] drew attention to the similarity between the experimental shocks of histamine and of anaphylaxis, efforts have been made to synthesize substances antagonistic to histamine. In the meantime Code,[2] Rocha é Silva,[3,4] Dragstedt,[5] and others have presented additional evidence for the role of histamine in allergy as well as in anaphylaxis. The earliest reports of success in the search for antihistamines came from Bovet's laboratory when the so-called Fourneau series of synthesized phenolic ethers were described

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From The New York Hospital and the Department of Medicine, Cornell University Medical College.

in 1933[6] and in 1939.[7] Although these products exhibited definite powers to antagonize histamine *in vitro* and *in vivo*, they proved too toxic for human use. The difficulty was first surmounted in Antergan which Halpern[8] tested in man during 1942. This success of the French school motivated a further search for superior agents by American workers, and resulted in the introduction of Benadryl[9] and of Pyribenzamine[10] in 1945. At the time of the present writing, over a dozen such agents are available to the medical profession.

The aim of this presentation is to summarize the pertinent observations concerning these drugs and to present our own experience with a number of them in the control of hay fever.

Pharmacology

In reviewing the chemical and pharmacological properties of antihistaminic substances, certain rules laid down by Staub[7] have been found to govern the relationship between chemical structure and physiological activity. In general, the agents can be placed in one of two categories; (1) amines represented by the formula

$$R\text{-}N(R_1)\text{-}CH_2CH_2NEt_2$$

and exemplified by Antergan, PBZ, Neoantergan, Hetramine, Antistine and Thephorin; and (2) ether types represented by the formula

$$R_2\text{-}O\text{-}CH_2CH_2NEt_2$$

exemplified by Benadryl and Linadryl. In these formulae,

R represents phenyl or substituted phenyl
R_1 represents alkyl or aralkyl
R_2 represents phenyl or substituted phenyl

The amine or first group is said to be more "specific" against histamine shock, whereas the ether type is more effective against histamine-induced asthma.

The pharmacologic effects of the typical histamine antagonist have been summarized by Loew.[11] It blocks the bronchio-constriction caused by histamine, negating as many as 1500 lethal doses of histamine for the guinea-pig; it prevents the histamine contraction of both intestinal and uterine muscles; and it antagonizes the drop in blood pressure which follows histamine administration in the experimental animal. Not only does the antagonist exert these influences on the histamine reactions of animals but, in several species at least, has a parallel effect on anaphylaxis.

The use of the antihistamine as a pharmacological tool has, therefore, provided evidence which establishes even more firmly the concept that histamine plays a role in anaphylaxis in some animals.

In the case of man, the value of antihistamines has been amply established for certain allergic states (including the skin-test response). It is pertinent, Loew comments, that favorable reports have thus far been restricted to allergic diseases and a few other conditions where histamine is a suspected etiological agent. The implication is thereby given that histamine is involved in several types of human hypersensitivity. The low order of efficiency found for asthma, on the other hand, suggests that its mechanism differs from that of hay fever.

The antihistamines do not achieve their effect, it appears, by eliciting pharmacologic effects which oppose those of histamine. They differ basically, therefore, from epinephrin. In these agents, as Gilman[12] states, "we do not have compounds that cause, by themselves, any prominent degree of muscular relaxation [in the bronchi and gastrointestinal tract] or have any effect on the peripheral vasculature in their own right. We are dealing here not with physiologic antagonists, but rather with a type of blocking agent. The mechanism of action is similar to that by which atropine can block the effects of acetylcholine or of cholinergic nerve impulses. It does not prevent the release of histamine, but rather it prevents the histamine from gaining access to the receptor mechanism in the cell and there exerting its characteristic effects. I think if one keeps that mechanism in mind, many of the rather paradoxical failures of antihistaminic therapy will explain themselves." Gilman's remarks are in keeping with the observation that the gastric secretagogue effect of histamine is not antagonized by the new drugs—a situation which suggests that it is the receptor cell rather than histamine itself which is blocked when the drug exerts its typical influence.

Toxicity

In animals, toxic doses of all the antihistamine drugs lead to central stimulation as evidenced by hyperexcitability, tremor and convulsions. The commonest side effect in man, on the other hand, is sedation. It is pertinent that the acute toxic effects of the antihistamines appear unrelated to any physiological mechanism involving histamine.[9] No signs of chronic toxicity have been observed in the blood, urine, parenchymatous organs, nervous system or bone marrow of man or animal.

TABLE I

THE THERAPEUTIC EFFECTIVENESS OF 11 HISTAMINE ANTAGONISTS IN COMMON ALLERGIC DISORDERS

ANTAGONISTS	Urticaria & Angio-edema		Extrinsic Rhinitis		Contact Dermatitis		Atopic Dermatitis		Intrinsic Rhinitis		Pruritus		Bronchial Asthma		Migraine		Overall Incidence of Relief	
	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %	No. Patients	No. Relieved %
Antergan[17]	53	94	15	100					6	100	7	85	45	69			126	86
Trimeton[18-22]	56	84	442	81	2	0	6	83	61	66			104	47			671	76
Decapryn[19,23,24]	25	84	165	80	2	0	6	67	67	63			41	66			306	75
Pyribenzamine[19,20,24-29]	553	82	3,080	76			177	67	529	59	26	61	571	35	6	17	4,942	70
Thephorin[19,30-40]	97	66	942	76	69	65	74	50	341	71	12	92	330	51	12	17	1,877	69
Benadryl[20,21,26,29]	488	89	736	70	18	78	101	63	223	57	40	20	414	46	38	45	2,058	67
Neo-Antergan[19-21,25-27,41,42]	24	67	604	66					77	61			188	43			893	61
Hydryllin[20,25,27,43]	34	59	183	65					130	48			715	55			1,062	56
Antistine[19,21,25,27,44,45,46]	73	71	263	60	13	69	14	50	28	60			101	30			492	55
Neohetramine[21,25,47]	45	69	384	54	8	62	11	9	41	51			129	36	6	50	624	52
Linadryl[48]	22	86	50	40			9	67	9	66			49	45			139	52
Total No. Pts.	1,470		6,864		112		398		1,512		85		2,687		62		13,190	
Per Cent Relieved		82		73		65		62		61		48		46		37		66

Therapeutic and Untoward Effects of Oral Administration in Man

Dosage: Pyribenzamine, Neohetramine, Linadryl and Neo-antergan are usually dispensed in doses of 50 milligrams, whereas 100 milligrams are prescribed for Antistine, and 25 milligrams serve for Trimeton, Thephorin and Decapryn. Hydryllin is the proprietary name of a tablet containing 100 milligrams of Aminophyllin and 25 milligrams of Benadryl. Antergan has been used by a single investigator in doses of 40 to 80 milligrams daily. Although no reference will be made in the present writing to routes other than oral, certain of the antihistamines have been successfully given intramuscularly,[13] intravenously[14] and by local inunction (PBZ[15] and Thephorin[16]). The interval advocated between doses is ordinarily not less than four to six hours, depending upon the recurrence of symptoms. At times, double or half the conventional dosage is suitable.

The Therapeutic and Side Effects of 11 Histamine Antagonists: a Survey of the Literature

Therapeutic Efficiency in Man: Table I is a composite of published results from the use of 11 histamine antagonists in eight common disorders of presumed allergic origin.[17-48] The investigators are indicated by the reference numbers listed above each drug. As indicated by the averages given at the bottom of the table, the drugs in general show their greatest effectiveness in cases of urticaria and angioneurotic edema, 82 per cent of some 1500 trials bringing relief. The next most responsive condition was extrinsic allergic rhinitis (or hay fever) with a therapeutic index of nearly 75 per cent among 7000 cases. Contact dermatitis, atopic dermatitis and vasomotor rhinitis responded somewhat less spectacularly, between 60 and 65 per cent of tests proving successful. Since the number of observations on contact dermatitis is small, it is possible that its future position in the list of susceptible conditions may shift. This remark applies also to pruritus associated with disorders other than urticaria, for only 85 such cases have been observed under antihistaminic therapy. On the other hand, bronchial asthma of either extrinsic or intrinsic origin has been widely treated with the new drugs and takes its position low in the list, with a therapeutic index of less than 50 per cent. (Our failure to distinguish between the extrinsic

TABLE II—SIDE REACTIONS FROM 8 HISTAMINE ANTAGONISTS

ANTAGONIST	General Incidence of Side Reactions		INCIDENCE OF COMMONEST TYPES OF SIDE REACTION															
	Total No. Patients Observed	Per Cent with Side Reactions	Sedation		Gastro-intestinal		Central Stimulation		Dizziness		Headache		Vascular		"Allergy"		Miscellaneous	
			Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Neohetramine[21,47]	509	13%	58	11	29	6	21	4	2	½	4	1	0	0	13	3	2	0.4
Antistine[19,21,44]	221	22%	20	9	19	9	3	1	3	1	1	½	1	½	1	½	5	2
Thephorin[19,30-32,34-38]	1,589	24%	54	3	82	5	196	12	22	1	25	1	17	1	9	0.6	36	2
Pyribenzamine[19,28,29]	2,058	24%	242	10	181	9	63	3	67	3	55	3	19	1	19	½	38	2
Trimeton[19,21]	171	35%	49	29	3	1	6	4	0	0	6	2	0	0	0	0	2	1
Decapryn[19,24]	157	41%	56	36	3	2	4	3	5	3	3	2	0	0	1	½	6	4
Neo-antergan[19,21,42]	255	42%	100	39	15	6	0	0	4	2	4	2	0	0	0	0	5	2
Benadryl[29]	655	61%	315	48	52	8	65	10	46	7	0	0	19	3	6	1	47	7
Total	5,615		894		384		358		149		98		56		49		141	
Average Per Cent		29%		16		7		6		3		2		1		1		3

and intrinsic forms is referable to this common practice among the authors reviewed. It is our impression,[29] however, that this is irrelevant in the case of the antihistamines, since seasonal forms have proved to be almost as unyielding as the idiopathic, or infectious, types.) Although very few observations were to be found for migraine, this disorder appears to be another which responds poorly to the antagonists.

The overall efficiency of each of the 11 drugs was crudely judged by calculating the general incidence of relief for all eight of the allergic disorders. The results are indicated in the right hand column of Table I, the drugs being listed in order of their average efficiency. Several of these figures should be accepted provisionally since the observations behind them are too limited for final judgment. Antergan and Linadryl fall in this category, fewer than 200 trials being involved. Among the other agents Trimeton, Decapryn, PBZ, Thephorin and Benadryl appear to be more effective than the average of 66 per cent, shown at the foot of the last column. Neo-antergan, Hydryllin, Antistine and Neohetramine, on the other hand, fall below this crude standard.

In view of the fact that over half the published observations have dealt with hay fever, it is not surprising that the sequence in column 3 resembles that of the column for overall efficiency, Antergan ranking first, Trimeton second, and so on. There are some shifts in this order for the columns headed "Urticaria" and "Atopic Dermatitis," reflecting either unreliable data or selectivity in drug effect. Since the results for Antergan and Linadryl are based on one publication only, no evaluation can be made until other investigators report on these drugs. Neither bronchial asthma nor intrinsic rhinitis appeared to show any discrimination among the different drugs. The number of data on contact dermatitis, pruritus and migraine are insufficient for final conclusions. This difficulty and others encountered in the appraisal of the antihistamines will be touched upon later in the article.

Side Effects: A search was made for reports of side reactions among the publications reviewed in Table I. Although information was not always available, adequate material was at hand to determine the incidence as well as the type of side reactions for 8 of the drugs. Table II refers only to those publications which stipulated the nature of the side effects.

Of the various untoward responses, sedation was the most prom-

inent. Whereas the average incidence for all 8 drugs was 16 per cent, as shown at the foot of the column, it will be noted that Benadryl acted as a soporific in 48 per cent of trials. At the other extreme was Thephorin, which sedated only 3 per cent of its consumers. Decapryn, Neoantergan and Trimeton also possessed this tendency in rather high degree whereas Antistine, PBZ and Neohetramine caused drowsiness in but one out of ten trials. It should be remarked that sedation is not always an undesirable side reaction, being of value in pruritus and in insomnia due to allergic states.

Gastro-intestinal disturbances were next in order of frequency, being noted in 7 per cent of all the trials. Patients with disorders of the digestive tract should probably avoid Antistine, PBZ and Benadryl and choose antihistamines of low gastric toxicity; viz., Trimeton and Decapryn.

Under "Central Nervous System," we have included such manifestations of central stimulation as: general irritability, nervous tension, insomnia, palpitation, agitation, paresthesias, genitourinary disturbances, chills, blurred vision and diplopia. One or more of these were encountered in a total of 6 per cent of cases. Several investigators noted that Thephorin was particularly prone to cause nervousness and insomnia, a situation which is consistent with its high incidence of central stimulation (12 per cent).

Dizziness was next in rank, being encountered after 3 per cent of trials with all drugs. Benadryl, with an incidence of 7 per cent, was the chief offender, Decapryn and PBZ rating second with 3 per cent.

It will be seen that Benadryl produced no headaches in 655 trials and that Antistine caused but few. The general incidence of cephalalgia was not high, however, PBZ topping the list with an incidence of 3 per cent.

Less frequently encountered were vascular disturbances (including tachycardia, tendency toward bleeding, edema of skin, pallor, tinnitus, syncope, sweating and flushing). The accumulated incidence of such complaints amounted to about 1 per cent.

So-called allergy to the drugs was reported for an equal proportion of the patients. The disturbances consisted of eruptions, cough and dyspnea. We have recently seen generalized eruptions in two subjects following the ingestion of PBZ.

Less frequently described in the literature were a host of miscella-

TABLE III—RELATIVE THERAPEUTIC AND TOXIC EFFECTS OF VARIOUS HISTAMINE ANTAGONISTS

HISTAMINE ANTAGONISTS	*Incidence of Relief*		*Incidence of Side Effects*		
	No. of Patients	*No. Relieved (%)*	*No. of Patients*	*No. with Side Effects (%)*	*Rank*
Antergan[17]	126	86	140	25	(5)
Trimeton[18,19,20*,21,22*]	671	76	398	25	(5)
Decapryn[19,23*,24]	306	75	157	41	(8)
Pyribenzamine[19,20*,24*,25,26*,27-29]	4,942	70	2,276	25	(5)
Thephorin[19,30,31,32,33*,34-38,39*,40*]	1,877	69	1,559	24	(4)
Benadryl[20*,21*,26*,29]	2,058	67	655	61	(9)
Neo-Antergan[19,20*,21,25,26*,27,41*,42]	893	61	649	29	(6)
Hydryllin[20*,25,27,43*]	1,002	56	233	36	(7)
Antistine[19,21,25,27,44,45*,46*]	492	55	417	18	(3)
Neohetramine[21,25,47]	624	52	630	13	(1)
Linadryl[48]	139	52	250	17	(2)
Total	13,190		7,364		
Average		66		27	

* Used for "Therapeutic" data but, omitted from "Side Effects" on this table.

neous conditions, such as early or excessive menstruation, decreased libido, impotence, emotional depression, sore throat, fever, oral anesthesia, dry mouth, muscular twitchings and incoördination. The sum total of such reports amounted to 3 per cent for all drugs.

A larger set of figures was available for toxicity without reference to the type of side reaction. The data for an additional 1749 cases have been added to those of Table II and listed for all 11 drugs to make Table III. The purpose of this table was to afford a quick comparison among all drugs for toxic as well as therapeutic characteristics. Added to the side-effects data, therefore, are summaries of all therapeutic information found in the literature. The agents have been listed in order of their therapeutic rank. The toxicity rating is indicated in the right-hand side of Table III.

It will be seen that those three agents which possessed the lowest therapeutic power (Antistine, Neohetramine and Linadryl) showed

also the lowest toxicity. In the middle bracket were Antergan, Trimeton, PBZ and Thephorin, which produced side reactions in every fourth patient. The average incidence of side reactions was 27 per cent for all 11 drugs, the figure for Neo-antergan approximating this incidence. More toxic than the preceding were Hydryllin, Decapryn and particularly Benadryl.

Attempts to Improve Methods of Appraisal of Drugs: Although the foregoing analyses of clinical data from the literature throw some light on the relative desirability of the various drugs, a more reliable evaluation could be made if some of the many variables could be removed from the test. One of these is represented by the multiplicity of observers, each of whose judgment probably colored the appraisals. Arbesman,[25] for example, recorded only 30 per cent of patients relieved by Antistine, whereas Kaplan and Erlich's[46] figure for the same test was 92 per cent. If a single observer could evaluate a number of different drugs, this particular variable could be largely eliminated.

An even greater extraneous factor is involved when one attempts, as we have done, to estimate the efficiency of an antagonist by lumping together the results of its use in sundry allergic disorders. When a new drug is examined for its influence on hay fever, for example, and only in a limited way is studied for its effect on asthma, a higher therapeutic index is to be expected than if most of the trials are made in asthmatic patients, since it is established that bronchial allergy responds poorly to the antihistamines.

In an attempt to circumvent such variables, we recently evaluated six antagonists by alternating their use in a group of 113 patients with a similar clinical disorder, ragweed hay fever. The data were segregated not only according to the intensity of their symptoms but also according to the degree of relief afforded, as well as to the type and severity of side reactions. It was hoped that these more rigid criteria might bring to light superiority of any one antihistamine.

The results of these trials can be visualized in Graph A, which indicates the desirable effects in its upper half and the untoward reactions in its lower section. It will be seen that PBZ and Trimeton possessed almost identical powers to control seasonal hay fever, whether judged by their capacity to afford complete or partial relief. This is perhaps more readily visualized in the white areas of the upper part of the graph, which show that failures occurred in only 18 per cent of the

group after either drug. Trimeton offered complete relief of severe hay fever in a somewhat greater percentage of trials than did PBZ.

The untoward responses, dealt with in the lower half of the graph, were of a severe order in an equal proportion of cases given either drug, whereas somewhat fewer mild reactions were noted after Trimeton than after PBZ. On the basis of these observations, one might conclude provisionally that Trimeton was the slightly superior agent for hay fever.

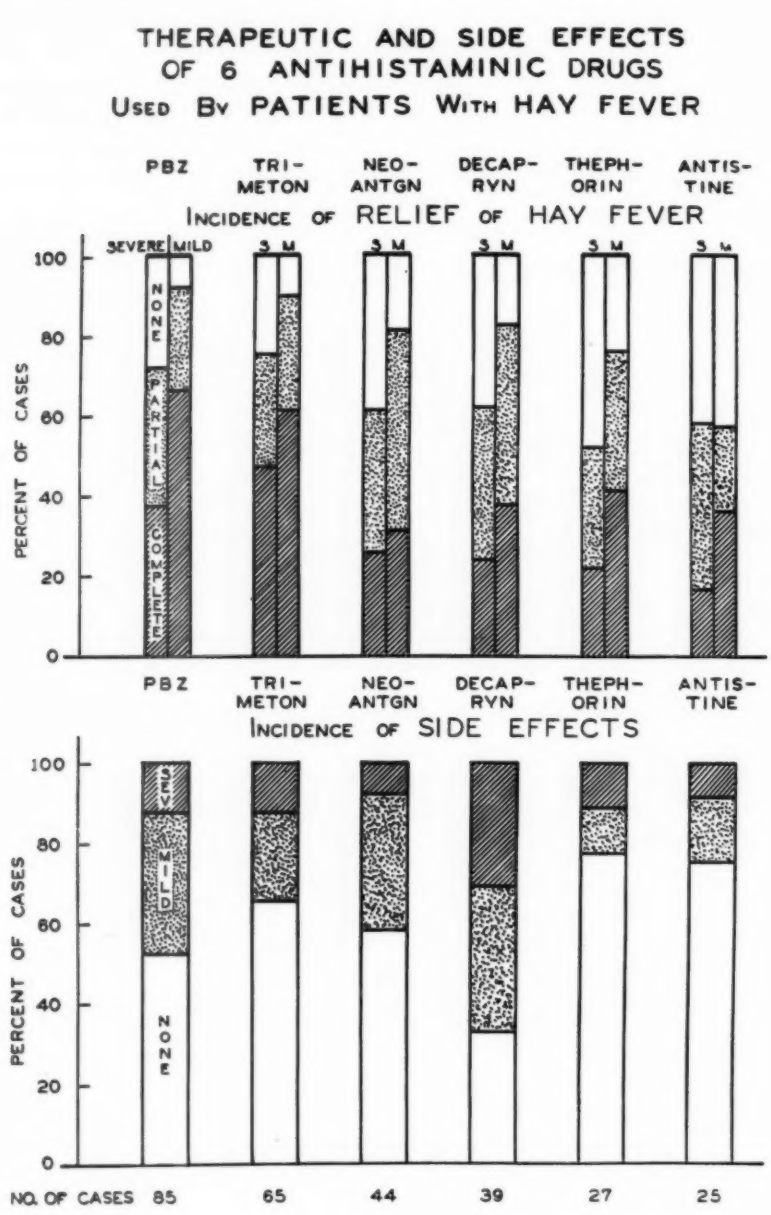
In making comparisons between Neo-antergan and Decapryn, the similar therapeutic potencies of these two drugs must be weighed against the definitely greater toxicity of Decapryn. The dosage of the latter should probably be modified because of this frequency of side reaction. In the case of the remaining two pharmaceuticals, Thephorin appeared to carry about the same ratio of undesired responses as Antistine but showed a greater therapeutic efficiency. Indeed, for mild attacks of hay fever, Thephorin approximated the control noted for Decapryn and Neo-antergan.

It is of interest in passing to observe that the side reactions of the antihistamines are in general of a mild order, as revealed by the dotted areas of the lower half of the graph.

When comparison was made between the order of therapeutic efficiency of the 6 drugs given our hay fever group and the order noted for the same agents in our review of the literature covering all forms of allergy, it was found that Trimeton ranked first in both series, whereas Antistine took last place. PBZ was listed second in the hay fever experiment, third in the overall trials. Decapryn and Thephorin ranked above Neo-antergan in the literature, below it in our series. Regarding the side effects, Antistine and Thephorin had the best records in both surveys, whereas Decapryn and Neo-antergan caused the most trouble. The relative positions of the other agents were at variance in the two tables.

Graph A is presented not only because it offers a quick means of judging the relative merits of different agents in hay fever, but also because it offers a simple form of presenting rather complex data. This handling might be adopted by future investigators to standardize their information and make possible the eventual selection of superior antihistamines. Placebos could of course also be used concurrently with the drugs to evaluate the psychic factor.

Since the appraisal of a dozen or more antihistamines is too large a


THERAPEUTIC AND SIDE EFFECTS
OF 6 ANTIHISTAMINIC DRUGS
USED BY PATIENTS WITH HAY FEVER
PBZ
TRI-METON
NEO-ANTGN
DECAP-RYN
THEPH-ORIN
ANTIS-TINE
INCIDENCE OF RELIEF OF HAY FEVER
SEVERE
MILD
S M
NONE
PARTIAL
COMPLETE
PERCENT OF CASES
100
80
60
40
20
0
INCIDENCE OF SIDE EFFECTS
MED
NONE
NO. OF CASES 85 65 44 39 27 25

Graph A

task for any individual to carry out single-handed, it is in order for a group of large clinics to undertake a joint, integrated attack of the problem. It is hoped that some of our suggestions for classifying the allergic disorders and the drug effects will prove useful to those who may organize such a project. At the same time optimal dosage should also be determined for the various antihistamines, since the doses in present use are probably too large for the more toxic preparations and too small for those with a low therapeutic index.

Summary and Conclusions

1. The histamine antagonists effectively negate many of the effects of histamine, anaphylaxis and allergy. In man they are particularly helpful as symptomatic aids in urticaria and hay fever, are also of definite but less value in contact and atopic dermatitis as well as in vasomotor rhinitis. Their influence on non-urticarial pruritus, asthma and migraine is less impressive.

2. Analysis of the therapeutic effects of 11 antihistamines reported in the literature reveals that among some 13,000 trials, Trimeton, PBZ and Thephorin offered the most satisfactory control of sundry allergic symptoms without an undue number of side reactions.

3. Final choice of the ideal antagonists, however, will have to await evaluation of multiple agents in similar groups of allergic patients under standard conditions and criteria, preferably through the concerted efforts of several large clinics. A small group of our hay fever cases, evaluating 6 antihistamines by alternation, found Trimeton and PBZ the most satisfactory from the viewpoints of therapeutic control and toxicity.

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MEDICAL AND SURGICAL TREATMENT OF PEPTIC ULCER*

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LITTLE that I can say on this time honored subject can be other than what I am sure could and would be said by any one of numerous outstanding physicians or surgeons in this city. The only novel aspect of such a talk lies in the suggestion that a physician, primarily interested in internal medicine, has been invited to present his views on both the medical and surgical aspects of this problem. It was for this reason alone that I was tempted by the flattering invitation from the Academy of Medicine, even at the risk of being thought impertinent and somewhat "out of bounds."

The orthodox story of peptic ulcer can be told quickly. By definition it is a chronic recurrent disease of unknown etiology. Characteristically peptic ulcer occurs in the proximal portion of the duodenum, but may be found in any portion of the stomach, the lower duodenum, the distal esophagus, in Meckel's diverticulum, rarely in the jejunum, and not infrequently in or near anastomoses between the stomach and the intestinal tract. Although the etiology is not known, certain facts have become clear in the course of many years of clinical experience with this malady. These facts have moulded the various therapeutic measures that are now currently employed in attempting to control the disease and to prevent recurrences. To date the word "cure" must be used with circumspection inasmuch as no method of treatment yet devised, however radical, can guarantee invariable, lasting success.

I should first like to discuss the medicinal treatment of uncomplicated duodenal ulcer. Because of the fact that so-called gastric hyperacidity is the general rule in duodenal ulcer and because of the added fact that experimental observations in man and in animals indicate the importance of this factor in conditioning ulcer activity

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and ulcer symptomatology, antacid therapy has long held a prominent place in the treatment of the disease. The declared purpose has been to neutralize gastric acidity and thereby reduce or abolish peptic activity. Complete neutralization is never obtained by any such means, except for limited periods of time. However, the pH of the gastric contents can be raised to a point at which peptic digestion is reduced to a minimum, and this state can be maintained for prolonged periods of time, provided the patient can and will tolerate the frequent and long continued administration of one or another of the various antacid preparations that are in favor at any given time. These range from simple bicarbonate of soda through the heavier free alkalis to such nonabsorbable preparations as magnesium trisilicate, the various colloidal preparations of aluminum, and the latest comers,—the resins. All are effective in reducing gastric acidity, and all are effective in controlling to a greater or lesser degree the pain or discomfort associated with most uncomplicated ulcers. The relief obtained by their use varies in duration and degree in individual cases, but there can be no doubt that they are useful aids as symptomatic measures, and their use may hasten the healing of active lesions. There can also be little doubt that they accomplish very little if anything in the prevention of ulcer recurrences. Certain disadvantages should be mentioned. Bicarbonate of soda, if taken in effective doses, can produce alkalosis, although this statement applies primarily to those individuals with ulcer who have an associated derangement of renal function. In those patients with prolonged massive hemorrhage or with real malnutrition secondary to partial pyloric obstruction, the use of sodium bicarbonate may provide the necessary factor to produce tissue edema in the presence of a lowered serum protein. The prolonged use of this antacid or of others which produce an alkaline urine may occasionally provide the basis for the formation of renal calculi. The continued use of many of these preparations may derange bowel activity to a point where diarrhea or severe constipation becomes a troublesome symptom. Thus magnesium, and less frequently soda bicarbonate, may increase bowel activity to a very undesirable extent. Calcium carbonate and some of the aluminum hydroxide preparations may cause constipation and even fecal impactions. Finally it may be stated that the administration of alkaline or antacid preparations at frequent intervals and over long periods not uncommonly becomes a monotonous and at times distressing

form of treatment to many patients. Under such circumstances they prejudice the success of otherwise effective treatment by constituting a source of increasing annoyance to an already disturbed individual. Their intensive use is not absolutely essential to the successful handling of the majority of ulcer patients.

Attempts to control gastric secretion by medical means have included many other measures such as the use of detergents, animal and vegetable mucins, x-radiation, hormonal therapy and the belladonna alkaloids. The detergents and mucins, although effective in adequate doses in diminishing peptic activity in the stomach, defeat their own purpose by the fact that they are extremely distasteful remedies from the patient's point of view. X-radiation, in order to be effective, involves certain risks, and at the best produces only temporary secretory changes. Hormonal preparations, such as pituitary snuff, antuitrin S, and the like, have failed to produce results that are of more than academic interest. Enterogastrone has not yet been purified. The available preparations have been used largely for investigative work, and sufficient time has not yet elapsed to permit a complete evaluation of this work. There seems to be little doubt that the prolonged parenteral use of this product has resulted in a reduction of gastric secretory and motor activity, with a beneficial effect on some ulcer patients. It is not yet known whether its use over many months will largely prevent ulcer recurrences, but recurrences have been noted during the course of continuous enterogastrone therapy by Sandweiss, ourselves and others. Alone of the therapeutic measures mentioned to date it offers the hope of usefulness in the prevention as well as the immediate healing of peptic ulcers.

Atropine and its derivatives affect secretory and motor processes in the stomach by reducing vagal stimulation of that organ. When *tolerance* doses are employed, either by mouth or by injection, ulcer activity can frequently be controlled by their use. Their action is temporary, but no more so than that obtained by the use of antacids. Actually the effects of proper single doses of atropine or belladonna can be noted over as long or longer periods of time than those due to single doses of many antacids. The use of atropine or its derivatives as effective agents in the treatment of patients with active duodenal ulcers is fully justified by clinical results and by careful pharmacological studies. Hypersecretion and hypermotility are both reduced, although

neutrality of gastric contents, of course, is not achieved. When combined with the usual dietary measures these anticholinergic drugs are frequently to be preferred to antacids because of the fact that their use by mouth involves fewer medications per 24 hours. Full tolerance doses, just short of dryness of the mouth or visual disturbances, are the only effective doses,—a point frequently overlooked. The disadvantages accruing to their use are well known. In addition to the two unpleasant symptoms already mentioned, headaches, disorientation, and difficulties in bladder control may occur,—objections that are particularly pertinent to the older age group. In the average case these unpleasant symptoms do not develop. It should be added that in active ulcers with a great deal of pain and moderate gastric stasis, subcutaneous atropine, given at regular intervals, may be of great help in tiding over a rather critical period. The synthetic preparations syntropan and trasentin are more expensive, much less reliable, and usually of little value as substitutes for atropine or belladonna. Incidentally, the frequent success attendant upon the proper use of atropine or belladonna preparations offers one solid reason for the use of vagotomy in carefully selected cases. In fact, the successful results obtained with atropine might be properly classed as medical vagotomies.

A third type of medication derives its therapeutic indications from the known relationship between states of emotional tension and gastric secretory and motor activity. Sedation, as provided by drugs such as phenobarbital, can at times be of profound help in controlling the symptoms of an active ulcer. It is a commonplace observation that ulcer patients can be symptomatically improved in short order if their emotional disturbances can be effectively controlled. I shall refer to the psychotherapeutic implications of this statement later. At least a partial block can be thrown across the abnormal stream of impulses going from higher centers through the hypothalamic area to those autonomic pathways supplying the stomach by the use of oral or subcutaneously administered barbiturates. In simple situations repeated, moderate doses of phenobarbital by mouth can be helpful to an important degree. In those patients whose ulcer pain and their own emotional unrest form a vicious cycle making symptomatic control very difficult, the regular, periodic subcutaneous use of sodium phenobarbital and atropine over a period of days may prove a therapeutic maneuver of major importance.

Other types of medication should be briefly mentioned, largely for dismissal. The use of histidine by parenteral injection has by now been thoroughly discredited. The fact that it is still used suggests either a rather blind hope on the part of a few physicians or a desire on the part of another few to indulge in wishful thinking at the expense of the patient whose weekly monetary contribution for treatments soothes the protests of critical professional judgments. In this regard it is wise to recall the excellent work of Sandweiss who obtained equally good or better results from the parenteral administration of sterile salt solution as from injections of histidine. The lessons to be derived from such careful observations are clear. Therapeutic methods which depend on gadgets, complicated maneuvers, injections, and expensive procedures may impress and temporarily help a patient afflicted by chronic disease. Their use is unjustified not only because of the fact that they are usually unnecessary, but also because they lead to ill considered thinking by the physician who uses them.

The second therapeutic approach to the problem of ulcer is that of diet. Numerous variations have been evolved which differ in detail but agree in one fundamental and common feature,—that of frequent, periodic small feedings. The Sippy diet, which frequently has been modified almost beyond recognition, depended on hourly feedings, day and night, of a milk and cream mixture. On the half hour heavy doses of alkalis were employed. Thus the patient theoretically had something by mouth 48 times in 24 hours. The milk and cream mixture, with its high fat content, resulted in an inhibition of gastric secretion; the milk proteins acted as a buffer substance as well as a supply of nitrogenous material. The addition of alkali tended to maintain a low level of secretory activity in the stomach. The regime, therefore, satisfied many of the requirements necessary for ulcer healing. It had certain real disadvantages. Many patients were unable to tolerate the cream feedings because of distaste or actual nausea. A further number found the interminable half-hourly feedings of milk and cream or alkali so distasteful after a few days that they refused to continue to follow the full schedule. As a result various changes have been made either in the type or variety of food, the frequency of feedings, or the constant alkali therapy. It is fair to say that practically all dietary measures have been successful in uncomplicated cases, provided that certain simple requirements are met. These requirements are common to all

ulcer regimens. They may be summed up briefly as follows. In uncomplicated duodenal ulcer any very simple nonbulky, nonirritating food that is fed frequently in small amounts, on time, is satisfactory. In an acute ulcer, hourly feeding intervals during the day, and two-hourly intervals at night, are usually effective in providing protein buffer, fat, and calories. Milk is still the best single food, but in most instances can be alternated with other simple foods to relieve monotony. As treatment progresses toward symptomatic improvement and healing, the intervals can be prolonged until the patient is on a simple six-meal bland diet. Frequently rest and dietary measures alone are entirely effective without the use of any medication.

Because a properly planned dietary regime can provide antacid, calories, and nitrogen, it has been inevitable that certain very special regimens have been devised for the treatment of ulcer embodying these general principles. Thus Co Tui introduced the idea of supplying nitrogen metabolic needs and at the same time an adequate gastric buffer, by using amino acid preparations for continuous oral or tube feeding during certain acute phases of ulcer therapy. Theoretically this type of treatment is effective because it meets caloric and nitrogen requirements, and at the same time introduces into the stomach a satisfactory buffer medium to reduce gastric acidity. It has the further advantage of supplying food in small bulk. I believe its chief value is in those cases where there is temporary or permanent narrowing of the pyloric orifice, and where there is a consequent and important state of malnutrition with loss of body nitrogen. It is possible that its use is also indicated in the period after severe hemorrhage when nitrogen reserves must be made up efficiently and rapidly. For the average uncomplicated case it is an unnecessary refinement, which is somewhat more expensive than need be and which presents the patient with the difficulty of ingesting a fairly unpalatable mixture. Furthermore, recent studies have cast serious doubt upon its efficacy as a buffer substance. Another specialized dietary maneuver is the constant milk drip by nasal tube devised by Winkelstein. Its effectiveness depends on the constant introduction into the stomach of a solution containing calorific material, fats and protein. It undoubtedly acts as a buffer solution, and there can be little doubt that it will work. To my mind it possesses no *real* advantages over simple oral feeding, except possibly in very special circumstances, and the presence of a constant inlying nasal

tube seems undesirable when simpler methods work just as well.

At this point it will be proper to comment on the so-called psychosomatic aspects of ulcer management. This is particularly pertinent because of the fact that none of the therapeutic measures that I have mentioned are in themselves sufficient, either alone or in combination, to provide protection against recurrences. For the energetic treatment of an active ulcer they are quite satisfactory, and their successful employment depends upon the experience and skill of the individual physician. In general, I think it is fair to state that an attempt should always be made to simplify their use as much as possible in a given patient. The easier therapeutic measures are made the more readily will the average patient submit to them, and the better the ultimate response. However, no regimen of diet, antacids, antispasmodics, sedatives, or any combination of them, will suffice to control the ulcer patient over long periods of time unless there is at the same time a profound understanding of the importance of the patient himself as an integral part of the problem. The original work of Beaumont, brought up to date by the very significant studies of Wolff and Wolf, made it possible to visualize the importance of emotional disturbances in conditioning gastric functioning. My own conviction is that we still cannot fully evaluate the significance of psychological disturbances on the ulcer patient. The evidence is still not clear as to just what role they play in the etiology of the condition. There can be no doubt, however, that in the patient who has an ulcer, behavior and situational problems are of tremendous importance in their influence on the course of the disease. Whether all ulcer patients should be classified as neurotics depends on a strict definition of the word neurosis. My own belief is that only a few are true neurotics; these constitute the small percentage of very intractable cases. But the vast majority are undoubtedly harassed, anxious, frustrated, resentful human beings, whose emotional tensions frequently dominate the entire problem. Orthodox psychiatric measures are not as a rule necessary for handling these patients, and this is indeed fortunate, because the supply of adequately trained psychiatrists would be found to be totally insufficient for caring for the very large group of ulcer patients. In certain cases expert psychiatric help is needed. In the majority of instances what is needed is a good physician with an interest in and an understanding of the intensely human problems that are so frequently

encountered. Such an interest involves time and an intellectual honesty which will not substitute pills, powders, and diet lists for the more time-consuming job of handling individual patients. This approach to the ulcer problem, which in large urban centers must also include the subsidiary help of social workers and dietitians, is the only approach that can be truly classed as preventive. To accomplish this the physician must be a good listener, a bit of a social worker, a bit of detective, and above all, a good doctor. The only approach to the problem of uncomplicated ulcer is the approach to the challenge of a chronic recurrent disease, and must include all of the factors that I have mentioned in order to succeed. If enterogastrone or some similar preparation, by prolonged use, does postpone or prevent ulcer recurrences over long periods of time, a very significant addition will have been made to our therapeutic armamentarium.

Up to this point I have limited my comments to a consideration of uncomplicated duodenal ulcer, which should be treated as a distinctive medical problem. The complications of duodenal ulcer are well known and demand special discussion. Essentially they are four,—perforation, obstruction, hemorrhage, and intractability. I shall take them in order.

Perforation of a duodenal ulcer demands immediate consideration of surgical intervention. I shall not dwell on the diagnostic features of this abdominal emergency; they are well known. There is general agreement that early surgical exploration and closure of the perforation constitutes the only proper form of treatment. Only when the perforation has been unrecognized for several days is surgery contraindicated and conservative treatment proper, with immobilization, parenteral feeding, the administration of full doses of morphine, and the use of adequate doses of antibiotics. Early perforation can be successfully treated by simple closure as soon as the condition is recognized, but time is of the essence. The energetic use of antibiotics is indicated, but is of secondary importance. One point needs constant repetition. The successful surgical closure of a perforated ulcer in no way solves the ulcer problem. It merely solves the abdominal emergency. The ulcer problem is essentially unchanged, although the occurrence of a perforation with subsequent successful surgery may properly raise the question of later elective surgery to preclude a recurrence with a second perforation. Second perforations are far from rare, and if elective surgery is planned, I am sure that subtotal gastrectomy is the method of choice.

Attempts to do more initially than simple closure of a perforated ulcer probably constitute bad surgical judgment.

The question of pyloric obstruction is somewhat less clear. When stenosis of sufficient degree has occurred, to preclude the handling of optimal quantities of food, then surgical intervention is an obvious necessity. About this there can be no argument. The difficulty that frequently arises derives from the definition of the word obstruction. Gastric stasis may occur secondary to an active ulcer in the gastric antrum, the pylorus or the duodenum. The appearance of obstructive signs and symptoms may be as great with no permanent stenosis as in those cases where fibrotic changes are marked. In the former instance they are due to spasm and edema secondary to an active ulcer and are usually amenable to intensive medical measures. In cases where important degrees of fibrous narrowing are present, medical measures are of no value except to aid in the proper timing and preparation for surgical procedures. For this the problem of obstruction, if handled first by a physician, should involve the use of several simple but rather rigid rules. No patient who is thought to be obstructed should be cared for by a medical man unless he at once sets definite limits to the period of what I would call therapeutic trial. The possibility of surgery should be at once recognized, and a tentative date for operation set. By so doing no valuable time is lost, and the measures proper for the treatment of partial and temporary obstruction will be fully effective in preparing the patient for surgery if such intervention is proved necessary. If the obstructive features have disappeared at the end of the allotted period, operation may be postponed or completely avoided as circumstances direct. Decisions should be the result of full coöperation between physician and surgeon, with full realization of the obligations of each in outlining treatment. Too frequently a partially obstructed patient is allowed to drift under medical therapy in the hope that the obstruction will slowly but steadily diminish. In such instances the usual result is a badly depleted patient who eventually is handed over to the surgeon in far from optimal condition. This patient is indeed a poor-risk subject, and the fault is entirely that of the medical man who does not recognize the importance of setting dates for critical decisions.

During the period of therapeutic trial in cases of obstruction, daily exact balances are absolutely essential. Initial blood chemistries deter-

mining blood electrolytes, serum protein values, nonprotein nitrogen, and possibly hematocrit figures and CO_2 levels must be combined with an accurate fluid balance chart. Too much stress cannot be placed on these fundamental measures. Measured gastric lavage at regular intervals, to determine the degree and trend of gastric stasis, must be consistent over a period of days. The type and quantity of oral feeding will obviously depend on the degree of stasis. Replacement of electrolytes, fluids, and calories in the form of dextrose and amino acid hydrolysates may be carried out quantitatively by intravenous administration. Plasma should not be used. The measures advocated by Co Tui may have a special bearing, to my mind, in this particular situation, and possibly may be used very effectively because of the low bulk, high buffer, high nitrogen values of the amino acid mixtures. In some instances the continuous milk drip might be equally effective, but only where the total bulk is not an important consideration. I might add that in many of these cases, where the obstruction is only temporary and secondary to an active ulcer, simpler measures with small frequent milk feedings, thorough atropinization and sedation are surprisingly effective. If under careful medical therapy gastric returns diminish, and replacement measures restore electrolyte, water and other deficits, then a decision against immediate surgery can readily be made after a proper interval. If progress is not favorable, as already mentioned, a decision for appropriate surgery can be made without loss of valuable time for preparation.

Repeated attacks simulating obstruction, or fully demonstrated stenosis, can be satisfactorily treated only by surgical measures. As a rule I feel sure that subtotal gastrectomy is the method of choice. There is an occasional poor-risk patient who may still be a candidate for posterior gastroenterostomy, but I believe this constitutes a very small number. The question of gastroenterostomy and vagotomy as a proper measure I shall discuss a little later. It is fair to say that the operative mortality following subtotal gastrectomy in properly prepared patients is extremely low when the operation is performed by adequately trained men. In the average case optimal results are obtained with about one week of careful preoperative preparation. In doubtful cases, a decision for or against surgery should be possible in this period of time.

The subject of hemorrhage is also somewhat controversial. Certainly the therapy of massive bleeding cannot be made a simple routine.

In general it can be said that the mortality figures from massive hemorrhage in patients under 45 are relatively very low, 1 to 2 per cent. In the later decades it is distinctly higher. Age alone does not supply the criterion that is to determine immediate or subsequent decision. The immediate problem in the treatment of massive bleeding is the treatment of shock. This can best be handled by the use of whole blood transfusions, given slowly, in sufficient quantity. Plasma should not be used. In older people, a low hemoglobin is less well tolerated than in younger individuals, and the hemoglobin probably is best raised to a level approaching 12 grams per cent. Rapid transfusions should be avoided unless rapid active bleeding is apparent, and then usually only as a preparation for emergency surgery. Sedation is generally indicated, but morphine as a rule is not the drug of choice because of the chance of increasing nausea and vomiting. Sodium luminal is often effective. Once shock is controlled, oral feeding should be initiated, using small, frequent feedings. The importance of this move was recognized many years ago by Andresen, forgotten, and rejuvenated by Meulengracht. The principle of providing a buffer medium, nitrogen and calories is still a fundamental one in this type of emergency. Just what type of food is to be chosen obviously is of little moment, except that it should be nonbulky, nonirritating, and capable at the same time of filling the above requirements. Andresen employed gelatin; Meulengracht used a fairly generous display of high protein foods, including meat. Co Tui has employed amino acid mixtures; Winkelstein a constant milk drip. All these measures work. My own experience leads me to believe that the more complicated measures are rarely necessary, although I am sure they may be indicated in an occasional instance. At the risk of being called reactionary, I still prefer simple frequent milk feedings in most cases, because of the simplicity of the method. I might add that I have tried the various measures that I have attempted to discuss. Antacids, I believe, offer little and are better avoided if adequate feeding can be obtained. Antispasmodics by injection, given at regular periods, probably are just as helpful, without adding to the difficulties of oral feeding. Once bleeding has stopped, as it usually will, the patient should be treated according to routine accepted methods, and an approach made to future decisions. Incidentally, iron by mouth is, I think, contraindicated in the immediate recovery period. It usually is quite unnecessary, there being a reasonable quantity of

storage iron available, and it may be irritating to the gastroduodenal mucosa. In most instances, a major hemorrhage should be an indication for elective subtotal gastrectomy. Individual exceptions to this rule do not alter the thesis that recurrent hemorrhages are to be expected. Certainly a second hemorrhage should force the decision. If hemorrhage does not cease, or recurs immediately, then in most instances a decision in favor of emergency surgery should be made if properly trained gastric surgeons are available. If they are not, the risk of surgery at this juncture is greater than the risk of continued medical treatment. In trained hands, supported by modern measures, subtotal gastrectomy may be properly advised. Such a decision is an individual one, however, and should be made as early as possible in critical cases. One maneuver should be mentioned. In patients with massive bleeding, where the source is not known, early x-ray examination, *without manipulation*, may define the problem immediately, without any appreciable added risk.

Possibly the most difficult problem is that of the intractable ulcer. Without discussing it in too great detail I should like to emphasize two points. Elective ulcer therapy has only a single aim,—the rehabilitation of the patient with the greatest protection of the patient from recurrences. If medical treatment cannot do this, regardless of the underlying reason, with few exceptions surgery should be performed. This is especially true because the risk of gastric surgery as an elective measure has been reduced to a figure of 1 to 2 per cent when the surgeon is well trained. In the presence of other serious disease, such as severe nephritis, advanced cardiac or pulmonary disease, obviously surgery may not be a proper move. One exception to choosing a surgical approach in this group of patients should be noted. A small number of ulcer patients do not respond to treatment because of a co-existing intractable neurosis. Otherwise proper operative measures will nearly always fail when applied to these patients. The ulcer may be controlled, but the patient is still a hopeless invalid, who has a new cause for further disability,—a major surgical procedure. Surgery should be avoided in these cases.

In the time remaining I wish to discuss two points,—ulcer surgery as such, and the problem of gastric ulcer.

The success of any elective operative procedure for chronic disease must be judged from several standpoints. Immediate mortality figures

are the first consideration. With special exceptions, the operative risk has been steadily reduced until in well-trained hands it is in the vicinity of 1 to 2 per cent. This is true of gastroenterostomy, subtotal gastrectomy, and vagotomy. The pertinent question, therefore, is one concerning the end-result. Evaluation of any form of ulcer surgery requires *many* years of careful follow-up, which should concern itself primarily with two points: 1) ulcer recurrence and 2) the general overall result of health or disability. It does little good to prevent ulcer recurrence if the patient is left an invalid.

In the case of simple gastroenterostomy, the experience of the last 30 years has convinced most of us that this operation does not prevent recurrent ulcer with sufficient surety to justify its use as a routine procedure. Although figures vary in different clinics, the general thoughtful consensus is that reactivation of duodenal ulcers, or the formation of stomal or jejunal ulcers, is altogether too frequent to warrant the use of gastroenterostomy in any but an occasional patient. Anastomatic ulcers probably result in at least 10-15 per cent of all cases that are carefully followed, although individual statistics range from 1 to 40 per cent. The experience with subtotal gastrectomy also varies, and precise follow-up figures are still to be awaited. Probably the most careful and critical follow-up is that from the Mount Sinai Hospital of this city. I imagine that further evaluation will reveal that in subtotal gastrectomy for duodenal ulcer, if the pyloric antrum has been completely removed, anastomatic ulcers may be expected in approximately 5 per cent of the cases. The complete removal of the pyloric antrum is, I believe, a measure that is essential for optimal results. In our experience at the Massachusetts General Hospital the incidence of stomal ulceration is very high in those instances where even a small portion of the antral end of the stomach remains. There are times when complete removal is technically very difficult because of the amount of inflammatory reaction in the neighborhood of an active ulcer, and in these instances experience has shown that a two-stage procedure may be of immense value, inasmuch as it enables the surgeon to carry out the actual resection of the pylorus and proximal duodenal area at his leisure after the acute inflammatory process has completely subsided. The incidence of recurrent ulcer following the procedure of vagotomy is not known, due to the fact that a critical follow-up on a sufficient number of cases is not available. Five years

at least, and preferably 10 years, must elapse before any adequate information is available. In our own series, in which a careful follow-up is being caried on by Moore, recurrences have been seen in approximately 5-6 per cent of the cases operated during the last 4 years. Obviously enough time has not yet elapsed. It can be said, however, that no surgical procedure has completely solved the problem, although such a statement in no way militates against the enthusiastic use of present surgical measures in properly chosen cases. One must insist, however, that following surgery the patient must still take reasonable care of himself, with special reference to regulated eating habits, the unwise use of alcohol, and the avoidance of prolonged serious nervous tensions.

The evaluation of operative therapy must go further. Even without ulcer recurrence, is the patient still bothered by annoying symptoms as a result of his operation? As regards subtotal gastrectomy, two facts are worthy of mention. The so-called "dumping syndrome," which follows this operation in from 10 to 15 per cent, occasionally becomes a major symptom and, because of its severity makes the patient as great an invalid as he was before surgical intervention. The exact mechanism of this phenomenon is not fully understood, but it probably involves motor and vasomotor disturbances occurring as the result of rapid jejunal filling in an over-reactive patient. It rarely occurs in stable individuals, and it may represent a true neurotic manifestation. Atropine in full doses before meals and frequent feedings of small bulk and low in sugars sometimes help. Although it frequently simulates a hypoglycemic reaction it is very improbable that a sudden reduction in blood sugar initiates the phenomenon. Fortunately it occurs as a major symptom in very few cases.

An equally or more important sequel of subtotal gastrectomy is that of faulty nutrition of sufficient degree to cause an important loss of weight with its accompanying loss of strength and endurance. I believe that such a result is to be found in about 15 per cent of cases. In approximately 85 per cent of cases there are no nutritional disturbances, and a satisfactory explanation of the occurrence in the 15 per cent of patients is not yet available. In all probability several factors are operative. Frequently these individuals have pronounced neurotic traits which influence their appetite and tolerance of food. I think nearly all of the patients are of the slender, over-active type, whose

daily metabolic requirements are augmented by constant muscular activity even when relatively inactive. Stool studies in carefully controlled experiments indicated increased loss of fats in the feces, with resulting loss of caloric material. Probably all these factors operate to make these patients serious medical problems, and to invalidate what otherwise would have been successful surgery.

A further word concerning vagotomy. This procedure is still too recent for complete evaluation. For proper appraisal it should be used only in unobstructed duodenal ulcers in patients who have been resistant to good medical therapy. Unless the procedure is thus limited no adequate judgment can be made of its particular contribution to ulcer therapy. If combined with gastroenterostomy, it may be a valuable procedure, but the combined operation precludes any final judgment on vagotomy. It should never be used for gastric ulcer. If performed, it must be followed with extreme care in order to fully study the final results. At least 3 to 4 years more are needed. It should be remembered that vagotomy in a sense represents a physiological procedure which aims at controlling gastric secretory and motor activity, rather than an operation which resects an important organ to remove gastric responses. The side-effects of vagotomy are fulness, heaviness after meals, diarrhea, and so forth, and are encountered as transient, mild phenomena in 15 to 20 per cent of cases. In somewhere between 5 and 10 per cent these disturbances may persist for months and may constitute major disabling symptoms. In the experience of Moore and myself they eventually subside. Those symptoms associated with poor gastric emptying can be successfully treated with urecholine, as proposed by Miller and his associates. The recurrences of duodenal ulcer that we have encountered have been easily handled, and usually followed very gross dietary or alcoholic irregularities. As one patient put it, the operation provided good armor-plate protection that could be penetrated if the shooting got heavy enough! At present Moore and I feel that the procedure should not be used for mass production, but only for a few carefully selected and carefully followed cases. This point is worthy of emphasis because to a good thoracic, or very well trained abdominal surgeon, it is a relatively simple and safe operation. One additional point is to be made. At present it represents by far the best method for the successful treatment of gastrojejunal ulcer.

A last point of discussion is the question of gastric ulcer. This controversial subject still needs clarification. I can merely present my own convictions. Despite the ease with which benign gastric ulcer can be controlled medically, I am firmly convinced that every patient with gastric ulcer warrants a consideration of surgical intervention because of the danger of unrecognizable cancer. No medical man has the right to decide in favor of medical treatment unless he is fully prepared to follow the patient closely and indefinitely. If there is doubt after careful x-ray or gastroscopic examination, if there is evidence of failure to heal after careful treatment, if there is histamine achlorhydria, if the ulcer is in other locations than the classical mid-lesser curvature, —surgery to my mind is mandatory and should involve adequate resection. Diagnostic errors may be further reduced by the study of gastroscopic biopsies, and by cytological means of gastric contents by the Papanicolaou method. I do not believe, as some do, that all gastric ulcers should be resected, but I am sure most of them should. One reason for so thinking is that even in the case of a benign ulcer, operative mortality is very low in good surgical hands and postoperative difficulties are minimal. Furthermore, the chance of diagnostic error in "doubtful" lesions is far from negligible. In a recent survey of the surgery of the last ten years at the Massachusetts General Hospital, Welch has shown that more than 10 per cent of the cancers of the stomach coming to operation were considered benign prior to surgical intervention. Only persistent, repeated, complete studies of gastric lesions by all diagnostic measures available will enable a physician to decide in favor of conservative measures in the treatment of benign gastric ulcer.

A further word as to the newer diagnostic procedures. Cytological studies of gastric washings, using the Papanicolaou technique, may provide further identification of doubtful lesions. In order to succeed, the material obtained by aspiration must be carefully collected, immediately spun at high speed, fixed and stained, and then examined by a microscopist who is very experienced in the method. In a recent series of patients so studied at the Massachusetts General Hospital by Ulfelder and Graham, 85 per cent positive diagnoses were made by this method. With further experience such a measure may help to differentiate benign from malignant lesions and may increase the number of early diagnoses. Similarly, carefully obtained gastroscopic biopsies may provide important diagnostic material in doubtful cases.

In a review of this very broad subject, I have attempted to point out the advantages and disadvantages, the indications and contraindications for various medical and surgical therapeutic measures that must be applied to the problem of ulcer. As a final comment, may I repeat what I hope I have implied,—namely, that favorable results can only be obtained by thorough and whole-hearted collaboration between physician and surgeon. Without this, ill-considered measures or half-hearted measures are employed and the results are totally inadequate for the patient afflicted with this chronic disease.

MODERN TREATMENT OF SYPHILIS, INCLUDING SYPHILIS OF THE CENTRAL NERVOUS SYSTEM*

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AT THE risk of carrying coals to Newcastle it seems advisable to consider certain important characteristics of syphilis before discussing its treatment. The early stages of the disease (primary and secondary syphilis) comprise a relatively benign, acute phase of the infection during which the body tissues react differently to the Treponema pallidum than during the late chronic phase. The early lesions of syphilis are infectious but non-destructive and self-limited. If early syphilis is not treated, within a maximum period of two years the infected individual develops a permanently altered reaction to the treponemes which comprises the late chronic phase of the disease. The late lesions are rarely self-limited and they are always destructive. Probably 60 per cent of untreated syphilitics never develop demonstrable late lesions during life and remain in the so-called latent stage. As is well known, however, it is impossible to determine in advance who will remain in the latent stage and who will develop demonstrable late lesions. Gummas and gummatous reactions may occur thirty years or more after infection.

If the early acute phase is untreated the infected individual, with rare exceptions, develops a permanent refractory state toward early lesions. In other words, whether cured or not two or more years after infection, reinfection with the T. pallidum may occur but it will not be followed by the appearance of early lesions. If, however, antisyphilitic treatment is received during the early phase, the permanent establishment of the refractory state toward early lesions is inhibited, and unsuccessfully treated patients may relapse or successfully treated patients may be reinfected with the development of early lesions.

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The immunologic differences between early and late syphilis are not confined to the establishment of a permanent refractory state toward early lesions. Positive serologic tests for syphilis (STS) can be reversed to negative by antisyphilitic treatment much more rapidly during the early than the late stages of the infection. Following successful treatment of early seropositive syphilis, quantitative STS show a rapid fall and in the majority of cases become negative within three to nine months, depending on how early in the course of the disease the patient is treated. Some individuals treated for early syphilis have low STS titers for more than nine months after treatment. Experience has proved that such patients do not represent failures of treatment and that they will finally become seronegative without further therapy unless relapse occurs in which case there is a sharp rise in the quantitative STS titers. The rapid drop of STS titers which occurs following therapy of early syphilis is rarely noted after treatment of late syphilis. In at least 75 per cent of late cases no therapy will reverse positive STS to negative within five years and some patients remain seropositive for life.

The above statements about the STS following treatment of early and late syphilis have long been valid but there are still differences of opinion and also misconceptions about the interpretation of persistent positive STS after treatment. In my opinion, the fact that STS remain positive for many years following treatment of late syphilis does not necessarily mean the persistence of a syphilitic infection. It is not within the scope of this paper to give reasons for this belief but it should be remembered that STS are not tests for the microörganisms of syphilis but for a globulin factor called reagin. All of the tests are based on the principle of identifying antibodies. Presumably reagin is an antibody but it is neither protective against syphilis nor is it absolutely specific for syphilis. Individuals vary greatly in the amount of reagin they are capable of forming and there is no relationship between the height of the STS titers and the severity of the disease. Following successful treatment of early syphilis positive STS, with occasional exceptions, become completely negative within two years, and the reversal of positive tests to negative is one of the proofs of cure of early syphilis. Following treatment of late syphilis, the failure of positive STS to become negative is in no way proof of the failure of treatment, and it is a serious mistake to treat late syphilis with the sole purpose of obtaining negative serologic tests.

More time might well be spent in clarifying the foregoing statements but the subject of this paper is the penicillin treatment of syphilis to which I now turn.

Difficulties in Evaluating Penicillin Therapy of Early Syphilis: No antisyphilitic agent has had such controlled studies of its therapeutic effectiveness as penicillin. But, in spite of carefully planned programs of therapy and record-keeping, the evaluation of penicillin therapy of syphilis has been handicapped by a number of uncontrollable variables. Both the quality and kind of penicillin preparations used during the past five years have changed so rapidly that the prolonged follow-up research needed to evaluate various schedules of treatment has been unable to keep pace with changes in the penicillin products. Of even more importance all statistics on the rapid treatment of early syphilis have been vitiated by the occurrence of many probable reinfections. The greater the reservoir of infectious syphilis the greater is the possibility of reinfection. In numerous communities where the most careful follow-up observations on treated patients have been recorded, the reservoir of infectious syphilis has altered significantly during the past five years.

Because the incidence of infectious syphilis in New York has declined notably within the past two years and because penicillin G does not vary in its therapeutic effectiveness to the same extent as the earlier amorphous penicillin, statistics recording the results of treatment of early syphilis during the past two years probably give a truer picture of the effectiveness of therapy than do those reported for the previous three years.

Variations in Penicillin Preparations: The original penicillin preparations used in the treatment of syphilis were all sodium, potassium or calcium salts of amorphous penicillin which were dissolved in water and injected at frequent intervals. In 1945 calcium salts of amorphous penicillin were mixed with oil and beeswax thus delaying absorption. By 1946 amorphous penicillin began to be replaced by crystalline penicillin G which is now used almost exclusively. Early in 1948 sodium or calcium penicillin G in oil and wax was replaced by the relatively insoluble procaine salt and a few months later procaine penicillin G in oil and 2 per cent aluminum monostearate became available for general use.

As is well known, aqueous solutions of very soluble salts of penicillin

are rapidly absorbed and excreted. To obtain continuous demonstrable blood concentrations of penicillin with doses of 20,000 to 80,000 units in aqueous solution, injections must be given every three or four hours. POB preparations were more slowly absorbed than aqueous solutions. Hewitt, Whittlesey and Keefer[1] found that the maximum blood concentration of penicillin after an injection of 300,000 units of crystalline sodium penicillin G in oil and wax occurred about 4 hours after the injection and in some cases levels of 5 units per cc. were found in the blood. Demonstrable blood concentrations of penicillin after an injection of 300,000 units of POB could be found for fifteen to thirty hours.

Following an injection of 300,000 units of procaine penicillin G in oil or water, Hewitt, Whittlesey and Keefer[1] found demonstrable blood concentrations twelve hours after administration in 100 per cent of cases and twenty-four hours after injection in 92 per cent. The maximum concentrations occurred about four hours after injection and varied from 0.08 to 2.5 units per cc. of serum.

Following an injection of 300,000 units of procaine penicillin (small size particles) in oil and 2 per cent aluminum monostearate, the relatively high blood concentrations of penicillin obtained with the more rapidly absorbed products do not occur but demonstrable blood levels of 0.03 units or more were found in 90 per cent of 173 cases for four or more days.[2]

Up to the present there is little evidence that brief high blood concentrations of penicillin are needed in the treatment of syphilis. The time during which penicillin is active in the body tissues, however, is of great significance in antisyphilitic therapy. Consequently the new very slowly absorbed penicillin preparations may well prove of great value in antisyphilitic therapy. Daily injections of these preparations are probably unnecessary. Thus the physician now has at his disposal a variety of penicillin products by means of which he can choose schedules of antisyphilitic therapy which will meet his own convenience and that of the patient. It should be recognized, however, that insufficient time has passed for the evaluation of treatment with procaine penicillin G in oil and aluminum monostearate. The data now available on the treatment of syphilis with penicillin consist entirely of follow-up studies of patients treated with aqueous solutions of penicillin and POB. The chief value of the data on treatment schedules with the earlier penicillin preparations is that they furnish us with a background for determining

the optimum total dosage of penicillin and the optimum time of therapy.

Treatment of Early Syphilis With Aqueous Solutions of Penicillin and POB in Eight Days: The earliest schedules of penicillin therapy assigned to us at Bellevue Hospital by the Syphilis Study Section of the Subcommittee for Venereal Diseases of the National Research Council called for such small total doses over an eight-day period that they can now be disregarded. From the early experience we learned that for an eight-day period of therapy total doses of less than 2,400,000 units of penicillin in aqueous solution or in oil and wax were unsatisfactory. At Bellevue Hospital after treating fairly large series of patients with total doses of only 600,000 to 1,200,000 units of penicillin in seven and a half days, a variety of treatment schedules using more adequate doses were used.

Table I shows the cumulative "failure" rates for seven treatment schedules, the time of therapy in all cases having been seven and a half to eight days.

Although the number of patients with early syphilis treated by each of the schedules is relatively large, when each series is broken down into four different categories, the numbers of patients treated for seronegative primary syphilis and of those treated for relapse or reinfection following previous therapy of early syphilis are too small for significant statistical analysis. Nevertheless, it is of interest to note the percentages of so-called failures in each four categories, if for no other reason than to observe the fallacy of accepting statistics at face value without taking every possible variable into consideration.

Cumulative "failure" rates are computed by a rather involved statistical analysis based on the number of patients actually followed up for varying periods of time and not on the number treated. "Failures" include all those who relapsed, were reinfected or were re-treated because of persistently high STS titers. Since the number of patients kept under observation usually declines over a period of years and since all patients requiring re-treatment are included as failures, regardless of when they were re-treated, it is obvious that the longer the period of follow-up, the higher the cumulative "failure" rates become. If as many as 40 per cent of the treated patients are lost within the first year after treatment, it is unlikely that cumulative "failure" rates give an accurate estimate of the failures among those who were not followed up. The fault does not lie with the method of computing "failure" rates but with the diffi-

TABLE I

	Seronegative Primary				*Seropositive Primary*			*Secondary*			*Retreatments of Infectious Relapses or Reinfections*		
	Months of Follow-up	*Number Treated*	*Number of Observed Failures*	*Cumulative Failure Rate**	*Number Treated*	*Number of Observed Failures*	*Cumulative Failure Rate*	*Number Treated*	*Number of Observed Failures*	*Cumulative Failure Rate*	*Number Treated*	*Number of Observed Failures*	*Cumulative Failure Rate*
1146 Patients Treated with 1,200,000 U. Penicillin (20,000 u. q. 3 hrs. for 60 doses) and 0.32 gms. Mapharsen. (Nov. 1944 to Dec. 1945)	36	91	15	20.9	214	38	26.9	743	153	33.1	98	21	38.4
807 Patients Treated with 600,000 U. Penicillin in Beeswax and Oil Daily for 8 days. (Aug. 1945 to July 1946)	24	62	5	9.0	182	25	18.3	455	72	25.0	108	15	19.2
236 Patients Treated with 2,400,000 U. Penicillin (40,000 u. q. 3 hrs. for 60 doses), 0.32 gms. Mapharsen and 5 Bismuths. (Mar. 1946 to July 1946)	21	20	1	1.3	64	5	9.1	137	21	21.4	15	0	0
256 Patients Treated with 2,400,000 U. Penicillin G (40,000 u. q. 3 hrs. for 60 doses). (July 1946 to June 1947)	17	32	1	3.2	47	4	9.9	167	18	15.7	10	0	0
251 Patients Treated with 2,400,000 U. Penicillin G (26,666 u. q. 2 hrs. for 90 doses). (July 1946 to June 1947)	17	23	3	18.4	60	6	14.7	154	14	18.3	14	1	25.0
223 Patients Treated with 4,800,000 U. Penicillin G (80,000 u. q. 3 hrs. for 60 doses). (July 1946 to June 1947)	17	14	0	0	26	4	22.3	97	12	18.9	86	12	18.8
228 Patients Treated with 4,800,000 U. Penicillin G (53,333 u. q. 2 hrs. for 90 doses). (July 1946 to June 1947)	17	14	0	0	37	4	11.4	97	8	12.3	82	8	13.4

* Cumulative failure rates are based on number of patients kept under observation and not on the number treated.

culty of keeping large numbers of patients who do not feel sick under observation for long periods. At Bellevue Hospital we have succeeded in keeping over 60 per cent of the patients treated on a research basis under observation for at least two years. Nevertheless, our statistics as well as those of most others who have reported on the long-term follow-up of patients treated for early syphilis are at best rough approximations of the true picture, and they fail to take into account the probable varying percentage of reinfection in different series of patients.

Table I shows cumulative "failure" rates for different schedules of therapy used at different times and consequently the periods of follow-up after treatment vary. To compare the first series in Table I with the last four series we should know the percentages of "failures" following a seventeen-months period of observation. The cumulative "failure" rates for the first series at the end of a seventeen-months period of follow-up were as follows: seronegative primary syphilis, 14.6 per cent; seropositive primary syphilis, 20.4 per cent; secondary syphilis, 24.4 per cent; re-treated patients, 18.8 per cent.

In spite of variations in the "failure" rates of the 7 different treatment schedules shown in Table I the differences are not statistically significant. If the numbers of patients in all four categories in each series are totaled, the cumulative "failure" rates for the various treatment schedules of early syphilis are about 20 per cent. Attention might well be called to the higher percentage of "failures" in the series treated with 80,000 units of penicillin G every three hours for 60 doses than in the series treated with only half that amount of penicillin at the same intervals. In my opinion the only way this appreciable, though not statistically significant, difference can be explained is by the higher incidence of reinfections in the group treated with 4,800,000 units than in the one treated with 2,400,000 units. Evidence for my belief that many of the so-called failures were actually reinfections is available but time does not permit such detailed analysis in this report. In previous publications I have considered the differentiation between relapse and reinfection.[3, 4]

From the statistics shown in Table I we can conclude: 1) treatment with 2,400,000 units of penicillin in aqueous solution (with individual injections every two to three hours) is as effective as when twice that amount of penicillin is used; 2) the addition of 0.04 gm. arsenoxide to a total dose of 1,200,000 units of penicillin in aqueous solution gives no

better results than 2,400,000 units of penicillin alone; 3) daily injections of 300,000 to 600,000 units of POB are as effective as 40,000 to 80,000 units of penicillin in aqueous solution injected at three hour intervals.

"Failure" rates of 20 per cent are far from satisfactory but in all probability the actual results were much better than the statistics indicate because no attempt was made to differentiate relapses from reinfections.

Treatment of Early Syphilis With POB in Fifteen Days: It was not until October 1947 that we extended the period of penicillin therapy for early syphilis at Bellevue Hospital from 8 to 15 days. The treatment schedule consisted of 15 daily injections of 600,000 units of POB. By the time this schedule was in use the number of early syphilis cases admitted to our service had declined from a high of over 250 a month in previous years to less than 75 per month. For a variety of reasons all of the patients treated for early syphilis were not placed on a research basis. Since October, 1947 we have observed for 8 to 15 months 134 patients treated for dark field positive early syphilis with 600,000 units of POB for 15 days. Of these 3 were re-treated because of new infections, each of the 3 having developed new chancres at different sites from their original primary lesions; 1 was re-treated because of a persistently high quantitative Kahn test 9 months after therapy and another patient will be re-treated for the same reason. It has been our practice to re-treat patients who have positive STS in serum dilutions of one to eight or more nine months after treatment.

I am by no means certain that the excellent results obtained so far with the fifteen-day schedule of therapy can be attributed entirely to the increased total dose of penicillin and to the prolongation of therapy. For reasons which I cannot take the time to give here I am convinced that we had a much lower incidence of reinfections in the more recent series than in any of those in Table I. It is also probable that as good results could have been obtained with daily injections of 300,000 units of POB as with 600,000 units because reports from other clinics have shown excellent results with daily injections of 300,000 units for fourteen to sixteen days.[5] But, in spite of my doubts concerning the comparative value of the various schedules of therapy for early syphilis on which we now have data, it now seems that the optimum period of penicillin therapy for early syphilis is about fifteen days.

As yet we have inadequate data on the use of procaine salts of penicillin in the treatment of early syphilis. There is every reason to believe, however, that procaine penicillin G in oil or water without aluminum monostearate is comparable in therapeutic effectiveness to POB. Procaine penicillin G in oil and aluminum monostearate, on the other hand, offers possibilities of very different time-dose relationships in the treatment of syphilis than either POB or procaine penicillin without aluminum monostearate. At present in coöperation with the Syphilis Study Section of the National Institute of Health three different schedules of therapy with procaine penicillin G in oil and aluminum monostearate are being used at Bellevue Hospital: 1) A single injection of 1,200,000 units. 2) An injection of 1,200,000 units once a week for two weeks. 3) An injection of 1,200,000 units once a week for four weeks.

Another year will be needed before the results of the above treatment schedules can be evaluated. Obviously they represent an important simplification of the treatment of early syphilis if they prove successful.

Treatment of Relapsing Early Syphilis: Following treatment of early syphilis patients may relapse with or without early infectious lesions. In the latter case the relapse is determined only by marked sustained rises in quantitative STS from previous levels (serologic relapse). Relapses and also reinfections may occur before or after the STS have become negative.

Referring again to Table I it will be seen that the cumulative "failure" rates of patients treated with at least 2,400,000 units of penicillin in eight days because of relapse or reinfection were similar to those of patients treated with the same amount of penicillin for original infections. Many of the patients re-treated were probably reinfected but unquestionably some patients with early syphilis require more prolonged treatment and possibly greater amounts of penicillin than others. So far on our service we have not found a single case of early syphilis that failed to respond to penicillin or failed to have a successful outcome of treatment provided relapses were re-treated with increased doses over a period of at least 15 days. An example of the results following re-treatment of repeated relapses after inadequate therapy is shown in Table II.

I do not advise that relapses of early syphilis be re-treated as shown

TABLE II

J. L., a white female 26 years of age, was admitted to Bellevue Hospital April 15, 1944 with darkfield positive secondary syphilis. She was first treated with 10,000 units of penicillin in aqueous solution every three hours for sixty doses. The reports of her quantitative STS at the time of and following treatment were as follows:

Serologic Tests

Date	*Comp. Fix. Titers*	*Quantitative Kahn Tests*	*Date*	*Comp. Fix. Titers*	*Quantitative Kahn Tests*
4-17-44	130	256	5-31-44	12	8
5- 3-44	47	64	6- 8-44	8	Not done
5-12-44	36	16	6-15-44	12	16
5-18-44	12	8	6-22-44	75	32
5-25-44	9	8	6-29-44	110	128

On 6-22-44 and 6-29-44 no lesions were found but a spinal fluid examination showed pleocytosis with 84/3 cells and a 1+ Wassermann test in .25 cc. of spinal fluid. She was retreated, 7-7-44 to 7-14-44, with 40,000 units penicillin in aqueous solution every six hours for thirty doses.

Serologic Tests

Date	*Comp. Fix. Titers*	*Quantitative Kahn Tests*	*Date*	*Comp. Fix. Titers*	*Quantitative Kahn Tests*
7- 7-44	160	128	10- 5-44	Not done	128
8-10-44	36	32	10-23-44	Not done	256
9- 7-44	36	16	10-24-44	120	Not done

No lesions were found at the time of her second serologic relapse. The spinal fluid complement fixation titer was 15; cells 160/3; total protein 26; colloidal gold test added to 94. She was retreated 10-23-44 to 10-30-44, with 40,000 units penicillin in aqueous solution every three hours for sixty doses and 0.3 gm. mapharsen (5 x .06).

Serologic Tests

Date	*Comp. Fix. Titers*	*Quantitative Kahn Tests*	*Date*	*Comp. Fix. Titers*	*Quantitative Kahn Tests*
10-23-44	120	256	1- 4-45	Not done	16
11-22-44	Not done	32	1-11-45	Not done	8
11-30-44	Not done	32	1-28-45	Not done	16
12- 7-44	Not done	16	2- 1-45	Not done	32
12-14-44	Not done	16	2-15-45	96	128
12-21-44	Not done	8			

On 3-5-45 a single darkfield positive papule was found on the right labium major and solitary papules were found on the left forearm and back respectively. Her spinal fluid tests on 3-6-45 were: Wassermann negative; cells 173/3; total protein 27; colloidal gold not done. She was retreated 3-15-45 to 3-20-45 with 50,000 units penicillin in aqueous solution every two hours for 180 doses—total 9 million units.

(TABLE II—*continued on next page*)

(TABLE II—*continued*)

Serologic Tests					
Date	*Comp. Fix. Titers*	*Quantitative Kahn Tests*	*Date*	*Comp. Fix. Titers*	*Quantitative Kahn Tests*
3- 5-45	120	256	10-11-45	3	3
3-20-45	82	128	11- 1-45	4	3
4-14-45	Not done	64	11-29-45	0	3
5- 8-45	Not done	64	12-17-45	2	3
5-17-45	14	32	1-16-46	Not done	3
5-25-45	Not done	32	2-27-46	Not done	3
6- 7-45	10	16	4- 3-46	Not done	1
6-14-45	10	16	6- 4-46	Not done	2
6-21-45	Not done	16	7-17-46	Not done	0
6-28-45	6	8	8-26-46	Not done	0
7-12-45	6	8	9-23-46	Not done	1
7-19-45	Not done	8	11- 8-46	Not done	0
8- 2-45	6	8	3-13-47	Not done	0
8-23-45	6	3	7-24-47	Not done	0
9-13-45	4	3	11-20-47	0	0
9-27-45	5	3	5- 4-48	0	0

The spinal fluid examinations on 8-2-45 and 9-23-46 were completely normal.

in Table II. A better plan is to re-treat a genuine relapse with from 6,000,000 to 9,000,000 units of penicillin over a period of at least two weeks. I see no reason why either bismuth or arsenicals should be used in the treatment of relapse unless a second treatment with penicillin fails or the original infection fails to respond to penicillin.

Treatment of Neurosyphilis With Penicillin: Early syphilis of the central nervous system, as a rule, responds readily to any type of good antisyphilitic therapy. But permanent arrest of late neurosyphilis is achieved in less than 50 per cent of cases treated with heavy metals and arsenicals. Prior to the advent of penicillin, fever therapy was the treatment of choice for all cases of late neurosyphilis. Yet, in spite of its recognized effectiveness, relatively few patients with neurosyphilis actually received fever therapy unless they had general paresis. Because of the difficulties in obtaining fever therapy many neurosyphilities continued to be treated on an ambulatory basis with potentially toxic drugs for years. From 1939 to 1944 every patient with active neurosyphilis

admitted to our service at Bellevue Hospital received fever therapy, most of them having been treated with malaria. We now have several hundred patients who have been followed up for five or more years after fever therapy. Since April, 1944 we have used penicillin exclusively for the treatment of all types of neurosyphilis, and we have found penicillin more effective than malaria therapy.

In evaluating the results of therapy for neurosyphilis we have used the spinal fluid examinations as the only reliable guide to the arrest of the syphilitic process.[6, 7, 8] Dattner, who was associated with Wagner-Jauregg when malaria therapy for general paresis was first used, has long believed that the best evidence of activity of a syphilitic infection in the central nervous system is the presence of increased cells in the spinal fluid. In active late neurosyphilis the pleocytosis is usually associated with increased total protein. Following successful therapy, the cells in the spinal fluid should be less than 4 per cu. mm. three to four months after treatment, and increased protein determinations should show a definite decrease. Over a prolonged period of observation, quantitative Wassermann reactions of the spinal fluid, increased total protein values and quantitative colloidal gold tests should show a gradual but continuous trend toward normal. More than five years may pass before the Wassermann reaction of the spinal fluid becomes completely normal after successful treatment. In our experience, following treatment of neurosyphilis, if the cells were normal and the other tests showed a definite trend toward normal values, re-treatment with either fever therapy or penicillin failed to hasten the reversal of abnormal spinal fluid tests to normal. Furthermore we have not found that additional antisyphilitic treatment improved the clinical symptoms and signs of patients whose spinal fluid tests showed no evidences of an active syphilitic inflammation in the central nervous system.

The spinal fluid tests are of such great importance in the management of neurosyphilis that every effort should be made to ensure accurate and careful laboratory tests. We have found that the best spinal fluid complement fixation tests for syphilis and the most satisfactory colloidal gold tests have been furnished by the New York State Department of Health laboratories.[9, 10] The New York State laboratories titer the spinal fluid complement fixation tests for syphilis in units in the same way that complement fixation tests of the blood are titered. They also do the new Lange colloidal gold test which gives

TABLE III—PENICILLIN SUCCESS AFTER MALARIA FAILURE

F.J.E. 50 W.M. General Paresis

Age 40—Three Years Routine Treatment

Test No.	*Date*	*Blood Wass.*	*S.F. Wass.*	*Colloidal Gold*	*T.P.*	*Pandy*	*Cells*
1	7-16-42	4+	4+	5555**	55	4+	140/3
	AUGUST 1943—TERTIAN MALARIA (5), TYPHOID (3) and MAPHARSEN (10)						
2	11-30-43	4+	4+	2211**	85	4+	800/3
	JANUARY 1944—20 PENTAVALENT ARSENICALS						
3	3-16-44	4+	4+	5554**	62	3+	70/3
	APRIL 1944—20 ADDITIONAL PENTAVALENT ARSENICALS						
4	5-22-44	4+	4+	No data	60	2+	26/3
5	10- 4-44	4+	4+	No data	62	2+	250/3
	OCTOBER 1944—4 MILLION UNITS PENICILLIN						
6	10-20-44	4+	150*	164***	46	2+	43/3
7	11-20-44	76*	110	154	47	1+	36/3
8	1-15-45	44	71	144	37	F.T.	9/3
9	4-10-45	39	80	122	37	V.F.T.	14/3
10	7-11-45	20	77	130	38	V.F.T.	3/3
11	10-29-45	21	70	133	34	V.F.T.	6/3
12	1-18-46	17	41	68	33	V.F.T.	6/3
13	7- 5-46	11	34	72	32	V.F.T.	3/3
14	10-25-46	10	37	79	28	V.F.T.	6/3
15	5-16-47	10	28	75	27	±	8/3
16	11-28-47	5	17	71	29	±	8/3
17	5-28-48	7	15	80	35	V.F.T.	6/3

* Titered in units.
** Readings of first four tubes by the older Lange method of colloidal gold test.
*** The figures given represent the sum of readings in all 10 tubes by new Lange method.

more constant readings than the old test and affords quantitative values by adding the figures for the reactions in all 10 tubes. I cannot take the time here to describe the new techniques of spinal fluid tests but I would stress the fact that in many hospitals and laboratories the techniques now used are outmoded and unreliable. Intelligent evaluation of treatment for neurosyphilis would be promoted, in my opinion, if the New York State laboratory techniques were widely adopted.

The spinal fluid tests are a much better guide to the effectiveness of treatment for neurosyphilis than are the clinical signs and symptoms.

The clinical response to treatment depends largely on the site and degree of permanent damage in the central nervous system. If important functioning parenchyma has been replaced by scar tissue it is manifestly impossible to restore normal function by antisyphilitic therapy.

There are still differences of opinion regarding the relative merits of malaria therapy and penicillin in the treatment of neurosyphilis, especially general paresis.[11-18] At Bellevue Hospital we are convinced that penicillin has caused clinical improvement similar to that obtained by fever therapy and we do not advise malaria or any other type of fever therapy unless penicillin treatment fails to produce satisfactory changes in the spinal fluid tests. Table III shows the spinal fluid findings in a general paretic who failed to have satisfactory response of the spinal fluid tests after malaria therapy but responded well to penicillin.

Of 376 patients treated for active neurosyphilis with penicillin alone and followed up for nine to fifty-four months, forty-three patients only were re-treated; thirty-two (8.5 per cent) having been re-treated because of relapse as shown by spinal fluid tests and eleven (3 per cent) having been re-treated because of an attempt to improve the clinical status of the patient, in spite of satisfactory findings in the spinal fluid. The dosage of penicillin varied from 2 to 9 million units and the duration of therapy varied from ten to nineteen days. The majority of relapses occurred in patients who received less than six million units over a period of less than fifteen days. When aqueous solutions of very soluble salts of penicillin were used, treatment with 40,000 units every three hours for 150 doses proved sufficient for most cases of neurosyphilis. Equally good results were obtained with daily injections of 600,000 units of POB for fifteen days. We are now treating neurosyphilis with 10 daily injections of 600,000 units of procaine penicillin G in oil and aluminum monostearate. With this treatment demonstrable blood concentrations of penicillin are found for five to seven days after the completion of therapy but we have no data as yet on a prolonged follow-up of any of these patients.

Treatment of Late Syphilis Other Than Neurosyphilis: Gummas and gummatous infiltrations have responded well to penicillin therapy at Bellevue Hospital and also in the experience of others except for 2 gummas, reported separately, which failed to heal after penicillin but responded to malaria therapy in one case and to mapharsen in the other.[19, 20]

The evaluation of therapy for late latent syphilis and cardiovascular syphilis is difficult because in most cases positive STS do not become negative for years after treatment and no antisyphilitic therapy can restore normal function to an already damaged aorta or heart. In the case of latent syphilis quantitative STS obtained at regular intervals after treatment will usually show a gradual trend toward normal values although fluctuations in titers are not unusual. Re-treatment is not advised unless the quantitative STS show marked, sustained rises in titers from previous levels.

All types of late syphilis can usually be treated successfully with from 4 to 9 million units of penicillin given over a period of two to three weeks. The data now available indicate that such therapy has accomplished as much as or more than two years of routine therapy with heavy metals and arsenicals.

Conclusions

Although penicillin is not a panacea for every case of syphilis it has proved superior to all other forms of antisyphilitic therapy both in safety and therapeutic effectiveness. An occasional case may require therapy with arsenicals or fever but in general 4 to 9 million units of penicillin given over a 15-day period will accomplish as much in the treatment of all types of syphilis as any other known therapy.

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THE RISE AND PROGRESS OF MEDICAL EDUCATION IN SCOTLAND*

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It is interesting to trace the spread of medical knowledge down the centuries, in space as well as in time, in geography as well as in history.

The progress led from Greece to Rome, then to the Moslem Empire; back again to Europe by way of Salerno, thence to Padua, Paris, and Leyden, and at last to Britain and America. As the centuries unfolded, the centre of medical education shifted from place to place, each new seat of learning contributing its quota to the accumulating mass of information. Scotland played a noteworthy part in this geographical march of medicine, and the story of Scottish Medicine since the beginning of the 18th century has often been told and is well known to most of you. Nevertheless the contribution of Scotland, prior to that time, is a less familiar, though no less important, chapter of medical history and for that reason it has been chosen as a subject which may be of some interest to the present distinguished company.

Medical Education has been, and may still be, regarded as one of the major activities of Scotland. Just as the Scottish marine engineer is to be found on all the Seven Seas, so has the Scottish medical man exercised his art in all quarters of the globe.

Of course, the story of systematic medical education in Scotland does not lead us back very far. The "qualified" medical man is a comparatively recent product; indeed, before the 16th century, the career of medicine was open to all who cared, or dared, to embark upon it, and even after regulations were framed, the standard of medical efficiency remained very uneven. After all, we must remember that the General Medical Council, which controls the practice of medicine in Britain, came into being less than a century ago. Before 1858 there was no Register of "duly qualified" practitioners of medicine.

As a background to the story of the beginnings of medical education, let me try to sketch the history of medical practice in Scotland from the earliest times.

We have very little information regarding primitive medicine among the ancient inhabitants of Scotland. There may have been a special class of Medicine Men during the Stone Age. Certainly some such persons had their place during the Bronze Age, if one may judge from such scanty evidence as is furnished by a trephined skull of that period. The healing art was probably in the hands of a priestly class, the Druids, as they were called. Medicine and Religion have always been closely interwoven among primitive races, and the earliest hospitals of which we have any record were the pagan temples of ancient Greece.

The medical practice of those ancient Scots, or Picts, as they were called, was influenced by various early invaders. The Roman Army possessed medical officers, and certain surgical instruments, similar to those of Pompeii, as well as memorial tablets, found in Scotland, are relics of the presence there of Roman military surgeons. Another influence, of considerably later date, was that of Saxon doctors or "leeches." In one of the oldest Saxon manuscripts, the Leech Book of Bald, dating from the 10th century, there is mention of a number of Scottish herbal remedies.

Early in the Christian era, a knowledge of medicine was fostered by some of the Saints, notably by St. Columba (563 A.D.—

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Iona) who had a hospital and a herb garden on the Island of Iona, and by St. Cuthbert (635-687 A.D.) who wrought wonderful cures in the South of Scotland and Northumbria during the 7th century. Doubtless those monks handed on to their disciples such knowledge as they possessed, because the care of the sick and wounded formed an important part of their duties.

In still later times, indeed as late as the 16th century, medical practice was a hereditary accomplishment handed down from generation to generation in certain families in the Western Isles of Scotland, notably in Islay and in Skye where the Macbeths and the McConachers were the accredited medical practitioners. They possessed manuscripts of the medical classics (Hippocrates, Galen, Avicenna, etc.) translated into the Gaelic tongue, some of which are preserved in the National Library of Scotland, in Edinburgh. Certain wandering scholars added to the medical knowledge of Scotland, such as Michael Scot (1175-1232) who, in the 12th century, studied and taught in the famous medical school of Salerno, and who brought back to his native country the current learning of the time, albeit interlarded with much magic and astrology.

Despite those praiseworthy efforts, there can be little doubt that in those early times the status of medicine was very low. In his History of Scotland, Tytler remarks that during the 13th century "the patient who fell into the hands of those feudal practitioners must have rather been an object of pity than of hope . . . it is probable that a sick or wounded knight had a better chance of recovery from the treatment of the gentle dames and aged crones in the castles whose knowledge of simples was great, than from the ministrations inflicted upon him by the accredited leeches of the times." Such was the condition of medicine in Scotland before the foundation of the universities and the establishment of systematic medical teaching.

Although their several histories overlap to some extent, it may best serve the purpose of the present lecture if one describes, each in its sequence, the rise and progress of medical education in the four Scottish centres of learning.

St. Andrews, 1411

The first Scottish university was founded in 1411, at St. Andrews, the ecclesiastical capital and a place of great importance. Although provision was made, in the original charter, for a Faculty of Medicine, there appears to have been little teaching of medicine until the 18th century. Medicine was merely one subject of the Arts course, and like Anatomy, was merely a part of that modicum of general knowledge regarded as essential to every well-educated man

The most famous Scottish medical man of the 15th century was William Schevez (1428-97). A native of St. Andrews, he had studied at Louvain, and so distinguished himself that on his return he became physician to King James III at a salary of "£20 per annum, a velvet gown and oats for two horses." Eventually, he became Primate of Scotland, in succession to Archbishop Graham whose career of self-seeking and mismanagement ended in his loss of reason, and who was treated, or virtually imprisoned, in Loch Leven Castle under the medical supervision of Schevez, a difficult position for Schevez, yet his tact and skill were equal to it. Schevez bequeathed his excellent library to St. Andrews University; many valuable incunabula there bear his signature.

Within the next 150 years, the three colleges of St. Salvator (1450), St. Leonard (1572) and St. Mary (1587), were founded at St. Andrews, as also were the Universities in Glasgow and Aberdeen, but there was little or no teaching in Medicine in Scotland until after the Reformation; then, John Knox laid down, in his Book of Discipline of 1560, that Glasgow should teach only Arts; Aberdeen, Law and Divinity; while St. Andrews was to be the Medical School for Scotland. This plan was never put into effect, and the only result was that St. Andrews continued for many a year to exercise the privilege of granting, or perhaps one should say, of selling, the degree of M.D.

Among those who took advantage of this arrangement during the 18th century were Jean Paul Marat and Edward Jenner. In 1772, the Duke of Chandos offered to St.

Andrews a sum of money to endow a chair of "eloquence." The University decided that a chair of medicine might prove more useful, and Thomas Simson was appointed. Simson and his early successors did little to adorn the chair, but the 5th Chandos professor, John Reid (1809-49), who was appointed in 1841, was a man of high attainment, whose death at the age of 40 was a great loss. Another distinguished Chandos professor, after the chair had become one of Physiology, was James Bell Pettigrew (1834-1908), whose studies of motion in animals and especially of the flight of birds, was of importance in the development of aeronautics.

Other new chairs were now created, and a Medical School was gradually evolved at St. Andrews University; although it did not become fully established until in 1897 it joined forces with University College, Dundee, which had been established in 1881.

Aberdeen, 1494

And now let us turn northward to Aberdeen, the third of the Scottish Universities to be founded, but the first to institute regular medical teaching at a time when there was no other organized medical school in Britain. Aberdeen may thus claim to be "the Cradle of British Medicine." One of St. Columba's disciples, St. Machar, was sent on a northward journey, with instructions to build a church at a spot where a river took the form of a Bishop's Crook. The river was the Don, which assumes this sinuous course near its mouth, and the church became St. Machar's Cathedral, destined to be more securely founded by Bishop Dunbar some centuries later. Bishop Dunbar, in 1532, was also the founder of a hospital which, however, was rather of the nature of a home for pensioners than an institution for the sick or injured.

In the 14th century, Aberdeen was a centre of learning which produced the first Scottish historian, John of Fordun (*Scotichronicon*), and the first Scottish poet, John Barbour (*The Bruce*). The medical practice of that time, as already noted, was largely in the hands of "skilly women," or of landowners or lairds who attended to the health of their retainers. It was in 1494 that Bishop Elphinstone secured the coöperation of King James IV of Scotland to establish the University of St. Mary's, which became King's College, in Old Aberdeen. King James, it may be mentioned, took a keen interest in science and medicine. He conducted many experiments in his laboratory at Stirling, and it is on record that he actually paid several of his subjects for the privilege of extracting their teeth.

William Elphinstone, when he became Bishop of Aberdeen in 1483, found that part of Scotland "unlettered, ignorant, and almost barbarian." As the first Principal, or President, he chose Hector Boece, or Boyis, who had studied in Paris, and who wrote a history of Scotland. The Universities of St. Andrews and Glasgow had already been founded by Bishops, and Elphinstone improved upon those efforts. His University was not to be a mere sanctuary for scholars but a real centre of culture for the north of Scotland. From the very start, provision was made for the teaching of medicine by the appointment of a "Mediciner" at a salary of £12 a year with the right of salmon fishing in the River Don, a valuable perquisite. The first Mediciner was James Cumyne. The third was Gilbert Skene, author of a little book on plague of which only one copy exists (in the National Library of Scotland). It was entitled *Ane Breve Description of the Pest* and was the first original medical work to be printed in Scotland. It is dated, Edinburgh 1568.

After the time of Gilbert Skene, the office of Mediciner at Aberdeen lapsed for a time, and the next event of importance was the establishment of a second University, in 1593. King's College did not favor the changes wrought by the Reformation, and in consequence, George Keith, Earl Marischal, a zealous follower of Calvin, founded this rival University which still bears the name Marischal College. The two universities continued to work separately until their union in 1860. The students of both colleges were strictly disciplined under the watchful eyes of the "Regents" as the professors were called. Students were obliged to commence work at 6 a.m. and to be in bed by 9 p.m., although once a week

they were permitted to amuse themselves on the links. From the start, Medicine was taught at Marischal College, the first professor being Patrick Chalmers, whose ledger, still preserved, shows that malaria was prevalent in his time.

In the 16th century, Duncan Liddell (1561-1613), a distinguished son of Aberdeen who had been educated at King's College, held for some years the Chair of Medicine and Mathematics at the University of Helmstadt and amassed a considerable fortune, part of which, together with his library, he bequeathed to Marischal College on his death in 1613. There is a beautiful brass plaque to his memory in the Church of St. Nicholas.

The next step in advance, in 1741, was the establishment of an Infirmary for "poor persons who have distemper upon their bodies and such others as meet with the misfortunes of broken bones." It contained 20 beds and was the forerunner of the magnificent infirmary opened in 1936 which cost exactly one thousand times as much money to build. Medical education was furthered by the Aberdeen Medical Society, founded in 1789 by Sir James McGrigor who became Director General of the Army Medical Service and was celebrated for the excellence of his Reports on the Health of the Army. The Society was really a sort of extramural school and candidates for membership were obliged to pass an entrance examination in Osteology, Greek, and Latin.

No account of Aberdeen medicine is complete without some reference to the family of Gregory, which produced sixteen professors in various Universities. The first of them was James Gregory, Professor of Mathematics at St. Andrews. His son, James, was Mediciner at King's College and was, in turn, succeeded by James the younger (son), then by John (brother). John became Professor of Medicine at Edinburgh in 1766 and was the father of James Gregory who succeeded him in the Chair, and who was the originator of the famous Gregory's powder.

The teaching of Anatomy was of high standard in those early days. Andrew Moir was lecturer in 1831, when there was strong feeling against anatomists owing to the nefarious doings of Burke and Hare in Edinburgh. Moir's dissecting room was burned down yet the lecturer maintained his prestige, continuing to teach until his death from typhoid fever at the age of 38. A later anatomist of great distinction was Sir John Struthers (1823-99), while Surgery was in the capable hands of Sir Alexander Ogston, who served abroad as a Surgeon in the war of 1914-18 and wrote an interesting book entitled "Memories of Three Campaigns." Aberdeen has had many other famous graduates, among them Sir Patrick Manson (1844-1922), "the father of Tropical Medicine."

Glasgow, 1451

Now let us glance at the third great centre of medical learning, that of Glasgow. In the 16th century Glasgow was a town of subsidiary importance, with a population of only four or five thousand. The University had been founded by Bishop Turnbull in 1451 but Medicine was not actively taught for a long time. Andrew Boorde, physician, monk and traveller, who in 1547 wrote the first original English medical book to be printed—*A Breviarie of Health*—visited Scotland during his wanderings and spent a year at what he called a "littyle unyversite named Glasco." This would appear to indicate that there may have been some medical teaching to attract him. Certainly there was a hospital, that of St. Nicholas, which had been founded by Bishop Muirhead in 1471, although very probably this was an almshouse, like Bishop Dunbar's hospital at Aberdeen. Later the Hospital of St. Nicholas came to be known as Provand's Lordship and it still stands—the oldest house in Glasgow—close to the Cathedral.

There was no organized control of the practice of medicine in and around Glasgow until the Faculty of Physicians and Surgeons was founded by Peter Lowe in 1599. At that date none of the Scottish Universities granted degrees in medicine but the Faculty was empowered to examine candidates and to decide whether they might be permitted to practice. Incidentally it may be remarked that Peter Lowe was a

Scottish surgeon who had served for over 20 years in the Army of France and had published in 1597 a *Discourse on the Whole Art of Chyrurgerie,* the first text book of surgery to be written in English. Peter Lowe's aim in founding the Faculty was to regulate and control medical practice in Glasgow. It was also resolved to give free medical treatment to the poor and even today this resolution is honored in spirit, if not in practice, since the Minutes of each meeting conclude with the words—"the poor were treated gratis, and the Faculty adjourned."

The teaching of Medicine in Glasgow University was very desultory and ineffective until the 18th century. The first professor of Medicine, Robert Mayne, was appointed in 1637 but he appears to have accomplished little. The real founder of the Medical School of Glasgow was William Cullen (1710-90). Born at Hamilton in 1710, he began his career as a general practitioner in his native town, in partnership with William Hunter. In or about 1744, Hunter went to London where he became a famous anatomist and obstetrician, and where he was joined by his more famous brother, John Hunter. Cullen meantime removed to Glasgow, and commenced his academic career as Professor of Medicine and Chemistry. With that versatility which was not uncommon at that day, he also taught Botany and Materia Medica. In 1755 Cullen was appointed Professor of Chemistry at Edinburgh, where later he succeeded to the Chair of Medicine on the death of John Gregory. Cullen was, in turn, succeeded by James Gregory of "powder" fame. Meanwhile the Glasgow Chair of Chemistry passed to Cullen's assistant, Joseph Black who, famous for his discovery of "latent heat," shares with Cullen the credit of establishing the Glasgow Medical School, which was well staffed and consolidated by the end of the 18th century.

The Royal Infirmary of Glasgow was opened in 1794, equipped with 150 beds and "two sedan chairs to convey patients to and from their homes." The end of the eighteenth century also witnessed the establishment of a second University, in 1796, by John Anderson, a man of great ability and energy who had been Professor of Natural Philosophy since 1757. He intended to include faculties of law, theology, arts and medicine, but the medical faculty was the only one which really flourished and in the early years of the 19th century it became a formidable rival to Glasgow University. There were more than 700 students in 1830. Some years later the name was changed to the Anderson College of Medicine, and this institution continued to serve a useful function as an "extra-mural" school.

Meantime there were many distinguished teachers in Glasgow including Allen Thomson who taught anatomy and physiology successively at Edinburgh and Aberdeen and who eventually became Professor of Anatomy at Glasgow in 1848. His administrative ability was of great service to the University.

Of course, by far the greatest figure of the Glasgow Medical School was Joseph Lister, who went from Edinburgh in 1860 to become Professor of Surgery, and who introduced his antiseptic principle in 1865. His first paper on the subject appeared in the *Lancet* on March 16th, 1867 and was entitled "A New Method of Treating Compound Fracture." Thirteen cases were described, with one death and one amputation —a remarkable result at a time when such an injury was attended by high mortality and was almost invariably treated by amputation. When Lister returned to Edinburgh as Syme's successor, the Glasgow Chair was filled by Sir George Macleod and he, in turn, was followed by Sir William Macewen (1848-1924), whose works on the treatment of brain abscess and on the growth of bone are classic accomplishments.

The Chair of Medicine, in 1862, passed into the able hands of Sir William Tennant Gairdner (1824-1907) who in the following year became Glasgow's first Medical Officer of Health. When he assumed office, one third of all deaths in the city were the result of infectious disease, principally typhus fever, but under his able control the health of the city improved greatly. There were many other great physicians and surgeons, but enough has been said to prove the importance of the Glasgow School of Medicine.

EDINBURGH

Finally, let me try to give a brief outline of the rise and early development of the Edinburgh Medical School. I have kept it to the end, as Edinburgh is the youngest of the Scottish Universities, founded in 1583. Nevertheless Anatomy and Surgery have been subjects of instruction at Edinburgh since the beginning of the 16th century. It was during the reign of King James IV of Scotland, who has already been mentioned as a patron of medicine, that the Barber Surgeons of Edinburgh obtained their Charter from the Town Council in the year 1505. The "Seal of Cause," as it was called, empowered the Barber Surgeons to decide, by examination, who was to practice within the Burgh. Candidates were to be able to "baith read and write" and were to be familiar with "the anatomy of man's body" and the position of the veins, venesection being then the treatment for many ills. Furthermore, the Incorporation of Barber Surgeons, which later became the Royal College of Surgeons of Edinburgh, was entitled to claim the body of one executed criminal each year for dissection purposes and, strangest of all regulations, was to have a monopoly of the sale of alcoholic liquor (aqua vitae). Unfortunately this monopoly has not been retained. The early meeting place of the Barber Surgeons was a mean street called Dickson's Close. There was some intermittent teaching of anatomy during those early days, but a great impetus to learning was given in 1583, when the Town Council established the Town's, or "Tounis," College So determined were they that their institution was to be free from what they termed "medieval papistry" that they did not apply to it the name "University." At first, there was no provision for the teaching of medicine, but an important step in advance was the foundation of the Royal College of Physicians in 1681 by Sir Robert Sibbald, who had studied at Leyden and who was the author of important works on history and geography, as well as Medicine. Sibbald and his young colleague, Dr. Archibald Pitcairne, were appointed Professors of Medicine in the Town's College in 1685 They were also instrumental in establishing the Physic Garden, then an important adjunct to the teaching of medicine, on the site of the present Waverley Station. It was the precursor of the present fine Royal Botanic Garden.

Pitcairne attained a European distinction when he was appointed Professor of Medicine at Leyden in 1692, an appointment which was then possible, as language difficulties did not exist because all teaching was conducted in Latin. Among his pupils at Leyden was Hermann Boerhaave, who succeeded him, and who became perhaps the greatest teacher of Medicine of all time.

In those days the links between Edinburgh and Leyden were numerous and strong. Firmest of all was that forged by John Monro, a surgeon in the Army of William of Orange, who was so greatly impressed by the Leyden methods that he resolved that Edinburgh should have a Medical School, conducted on similar principles. Accordingly, he educated his son Alexander at Leyden with a view to having him appointed Professor of Anatomy at Edinburgh. This ambitious plan proved most successful. Alexander Monro assumed the Chair in 1720, and thus became the "Father" of the Edinburgh Medical School. He was succeeded by his son, Alexander Monro, secundus, who was followed in turn by the grandson, Alexander Monro, tertius. Monro secundus maintained the tradition of his father, indeed he was even more distinguished, but Monro tertius was content to read his grandfather's notes, over a century old, to his class, without even deleting the remark, "When I was a student at Leyden in 1719."

The Monros held the Chair for 128 years. But there were other noteworthy anatomists. Sir Charles Bell (1774-1842) commenced and ended his career in Edinburgh, but most of his great work on the nervous system was carried out in London. One of the great Edinburgh teachers of anatomy was John Barclay (1758-1826), who was obliged to deliver the same lecture twice a day in order to accommodate his large class. He was succeeded by Robert Knox (1791-1862), an admirable lecturer whose classes were very popular, and a man of high sci-

entific attainment. Unfortunately, his career was clouded by his unwitting association with the Burke and Hare murders in 1828. One of Barclay's assistants who became a famous surgeon was Robert Liston (1794-1847). Robert Liston and James Syme (1799-1870) were closely associated as teachers of anatomy in Edinburgh until, in 1835, Liston became Professor of Surgery to University College, London, where he was the first surgeon to employ ether as a general anaesthetic.

The anaesthetic value of chloroform was discovered by the Professor of Obstetrics, Sir J. Y. Simpson, in 1847. Simpson was a versatile man, although his incursion into the field of surgery made him unpopular with some of his surgical colleagues. He was one of those who opposed Lister's ideas, alleging that the prevalence of septic infection was due to faulty hospital construction, or "hospitalism," as it was called.

The first medical man in Edinburgh to confine his practice to surgery was Benjamin Bell, who lived at the end of the 18th century, who wrote a well known textbook of Surgery, and who was the direct ancestor of Dr. Joseph Bell, the Edinburgh surgeon, the original of Sherlock Holmes.

Benjamin Bell was one of the earliest surgeons to the Edinburgh Royal Infirmary, which was opened in 1741 and provided for 200 sick persons "each in a distinct bed." Before that day it was not uncommon for two patients to occupy the same bed. The greatest Edinburgh surgeon before the time of Lister was Lister's father-in-law, James Syme, of whom it was said that he never wasted "a word, a drop of ink, or a drop of blood." When Syme failed to secure appointment to the Infirmary Staff he established a hospital of his own, and that hospital, Minto House, was the scene of the operation described in *Rab and his Friends* by Dr. John Brown, who was Syme's house surgeon.*

The wonderful work of Lister, continued at Edinburgh when he succeeded Syme in the Chair of Clinical Surgery, deserves a lecture to itself. Nor is it possible within the bounds of this outline, to discuss the progress of other subjects in the medical curriculum, the contribution to medicine of William Cullen, of James Gregory and, in later times, of Sir Robert Christison (1797-1882) and many others who taught various medical subjects in the University and in the extramural School of the Royal Colleges. As time went on, and as other Medical Schools became established, Edinburgh ceased to be the main centre of medical education in Britain, although it still maintains a high standard and attracts many students, both undergraduates and postgraduates. Among them there have been many American students ever since the early years of the eighteenth century when the torch of medical learning, re-kindled and strengthened by Leyden and Edinburgh, was handed on, across the Atlantic, to Philadelphia and to New York. The close friendship then established remains firmer than ever.

* After this lecture Dr. Douglas Guthrie presented to the Library of The New York Academy a copy of the first illustrated edition of *Rab and his Friends.*

SECTION ON MICROBIOLOGY

FEBRUARY 16, 1949

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Reading of the Minutes

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Alphonse R. Dochez
College of Physicians and Surgeons
Columbia University

Gregory Shwartzman
Chairman
The Mount Sinai Hospital

b. Research on the common cold
Norman H. Topping (by invitation)
Leon T. Atlas (by invitation)
National Institute of Health
Bethesda

c. Secondary invaders in reference to the epidemiology of the common cold
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Columbia University

Harry Most
Secretary
New York University
College of Medicine

Introduction to Studies on the Common Cold

A. R. Dochez

If we examine ancient accounts of disease we easily discover the description of a group of respiratory symptoms that exactly represents the clinical manifestations of what today we call the common cold. That it is an ancient disease and that it has continuously maintained its characteristic picture there can be very little doubt. The cold seems to be firmly established as a human disease whose character and high incidence have remained unaltered throughout the centuries. Its causative agent must therefore be, in the terms of Theobald Smith, a most efficient parasite.

For many years curiosity concerning the causation of the cold has remained active and has, especially during the period of modern bacteriology, stimulated the research activity of numerous investigators. With the development and improvement of bacteriologic techniques study of the throat and nasal flora of individuals suffering from the common cold has been the subject of repeated investigations. A number of well-characterized microörganisms have been described as being associated with certain outbreaks of the disease or with individual attacks. In general these organisms comprise Gram-positive cocci, Gram-negative cocci, such as Micrococcus catarrhalis, diphtheroid bacilli and a number of others. A specific causative relationship of these organisms to the disease has been difficult to establish convincingly because of their presence, without the production of symptoms, more or less continuously or for varying periods of time in the respiratory flora of healthy individuals.

In order to evaluate the pathogenic importance of the organisms mentioned above my colleagues and myself have studied a number of human subjects during healthy periods in order to gain complete familiarity with their nasopharyngeal flora. Later when any one of these individuals contracted a cold very careful bacteriological observations were made in order to ascertain if there appeared for the first time or in significantly increased numbers any easily recognizable organism to which a causative role might be assigned.

The results of these studies led us to certain conclusions. In the early days of the cold no new organisms appeared in the throat flora nor was there any significant increase in such potential pathogens as were already present. In fact, there generally appeared a diminution in the total number of organisms present, due in all probability to dilution by the increased amount of secretion. Whenever there was evidence of increased activity this usually occurred late and was frequently associated with some complication which had developed. Our observations led us to conclude that the common pathogens of the nasopharynx, in general, are not the initiating agents of infection of the respiratory tract of the type of common cold and that they act principally as secondary invaders of an inflammatory process causatively induced by a primary agent of unknown character.

With increasing knowledge of the pathogenic importance in infectious diseases of filterable viruses research turned toward the investigation of the possible relationship of such microörganisms to the common cold. Early important studies were those of Kruse[1] in 1914, Foster[2] in 1916, and Olitsky and McCartney[3] in 1923.

Kruse realizing the inadequacy of the evidence for a bacterial etiology studied the possibility of virus causation. He performed two experiments on students in which he inoculated the subjects intranasally with bacteria-free filtrates of nasopharyngeal washings from individuals with typical acute colds. In the first experiment positive results were obtained in four out of five volunteers. The incubation period was from 1-3 days. In the second experiment fifteen of thirty-six were positive in from 1-4 days. The incidence of spontaneous colds at the time was very low.

Foster in 1916 performed a similar set of experiments. Seven out of ten soldier volunteers were positive with one possible contact infection. Foster then attempted to cultivate the virus in Smith-Noguchi medium. Two strains were cultivated. The cultures showed a haze spreading from the area of the tissue. Small globoid bodies could be stained which appeared motile. Eleven volunteers were inoculated with the culture material and all manifested typical symptoms and characteristic appearance in the throat. Cultures from the subjects were positive for the growth of globoid bodies. Colonies were demonstrated in agar ascitic fluid. From what we know today the globoid bodies observed may have been due to small filterable Gram-negative bacteria which are constantly present in the normal throat. Some of these organisms are motile. It is possible that a true filterable virus was also present, which would account for the reproduction of the common cold in individuals inoculated with culture material.

Later studies[4] confirmed the transfer of colds from human to human by means of bacteria-free filtrates of throat washings obtained from individuals with colds. In at least one instance this infection was transferred from individual to individual in series.

In 1926 my colleagues and myself investigated the possible virus etiology of the common cold. Having learned from Dr. Francis G. Blake that chimpanzees were subject to colds resembling in every particular the human cold these animals were chosen as experimental animals. After establishing a careful quarantine, inoculation of bacteria-free material obtained from examples of typical human colds was performed. In a large percentage of instances the chimpanzees came down with colds similar in every respect to their own spontaneous colds and to the same infection in human beings. The cold could be passed from chimpanzee to chimpanzee using the established technique, and infection of healthy cage contacts also occurred. The incubation period of the disease was from 24-48 hours.

In view of the mild character of the experimental disease in animals, a similar study was made using human volunteers as subjects. The results obtained were essentially the same as those obtained with chimpanzees. The infection could also be transferred from human to human in series. The virus etiology of the common cold was thus established.

The next procedure was an attempt to cultivate the virus *in vitro*. Chick embryo medium was first used and the experiment proved successful. Large numbers of human beings were successfully infected with the tissue culture material and in one instance the culture remained infective for at least eighty transfers. Later the embryonated hen's egg was used for purposes of cultivation and successful experimental inoculations resulted. The number of egg transfers was relatively small, in one instance three and in another a few more.

No determinable changes could be observed in the medium in which the virus grew. All attempts to establish the culture virus in laboratory animals were failures. No significant tests for the presence of the virus in the culture medium could be developed either *in vitro* or *in vivo*. The virus was studied in many ways but no progress beyond animal and human inoculation took place.

The practical objective of this work was the development of a useful form of prophylactic inoculation. A number of individuals were injected with a living virus vaccine but successful immunization did not result. A number of facts militate against the success of such an undertaking, the lack of an enduring immunity following a spontaneous attack of the common cold and the absence of knowledge concerning the number of immunologic varieties of the virus of the common cold. Before further progress can be made there must be further development of the techniques for the study of the common cold virus and a great deal must be learned concerning the natural infection in man, particularly in respect to increased resistance to infection, if indeed such exists.

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Research on the Common Cold

NORMAN H. TOPPING

It has been 34 years since Kruse[1] reported that he had produced the common cold in human volunteers by inoculation of filtered nasal secretions from an assistant with a cold.

In the last 25 years great progress has been made in studies on viruses but up until the last 2 or 3 years there has been relatively little advance in our knowledge of the agent or agents of the common cold.

Kruse produced colds in 33 per cent of his first group of volunteers, the majority within 1 to 3 days after inoculation with a Berkfield filtrate of nasal washings. He was able to produce symptoms of common cold in 42 per cent of another group studied later, again the majority showing an incubation period of 1 to 3 days.

Foster[2] confirmed and extended Kruse's observations as to the human-to-human transmission of colds and its filtrable nature in 1916-17. In 1930 Long, Doull, Bourn and McComb[3] produced upper respiratory infections in 11 out of 19 human volunteers, using nasal washings from an individual with a cold, and the same year Dochez, Shibley and Mills[4] gave further confirmation, and also demonstrated the transmissability of human disease to anthropoid apes. Forty-four per cent of human volunteers and apes developed the disease syndrome; the humans exhibiting symptoms usually within 24 hours and the apes within 36-48 hours after inoculation. The infective agent was cultured under anaerobic conditions in the hashed tissues of 8-10 day old chick embryos.

The hashed-chick-embryo culture method of Dochez was confirmed by Powell and Clowes[5] in 1931. A variation of this method of cultivating the cold virus was reported in 1936 by Kneeland, Mills and Dochez.[6] Instead of using hashed-chick-embryo tissue, they described successful cultivation of the virus in the chorio-allantoic membrane of the developing chick embryo. The literature does not reveal later confirmation of this method for culturing the cold virus.

The pattern revealed in these reports of work done from the beginning of World War I to the period of World War II is one of confirming the existence of a filtrable infectious agent, or a group of such agents, capable of transmitting the common cold from an infected to a non-infected human under experimental conditions. Considerable ancillary research went forward, such as improvements in methods for obtaining the infective material, improvements in cultural media, and refinements in methods for preparation of the inoculum and its administration to volunteers. In addition, there were studies on the normal bacterial flora of the nose and throat, and on the variations in the flora occurring during colds. Various epidemiological studies were of interest to public health authorities but contributed little to the etiology of the disease.

During World War II the Office of the Surgeon General, U. S. Army, established a Commission on Acute Respiratory Diseases. Certain of the findings of this Commission may have considerable significance. One of the most important was the report[7] that two distinct common cold disease entities had apparently been discovered. The Commission demonstrated by experimental methods that two distinct types of minor respiratory illness could be transmitted to human volunteers. Among the several differences between the two diseases was the incubation period, i.e.—1 to 2 days and 5 to 6 days. Of even greater interest was the report that positive immunity was developed in humans against reinoculation with the virus of the disease characterized by a long incubation period, whereas no immunity was produced in volunteers reinoculated with virus obtained from an individual having the illness of short incubation period. Neither disease conferred immunity upon challenge by the apparent causative agent of atypical pneumonia.

The investigators felt that "these findings provide additional proof that at least two filtrable agents, or viruses, may induce minor respiratory illness in man, and suggest that these agents are probably distinct from the virus or viruses of primary atypical pneumonia."

An interesting report was made in 1947 by Pollard and Caplovitz[8] to the effect that they had succeeded in cultivating "the agent of the common cold" in the chorio-allantoic fluid of embryonated eggs. Subcutaneous inoculation with their cultured material in 2 doses of 1 cc. at weekly intervals was reported to have protected volunteers challenged intranasally with Seitz filtrates of nasal washings from naturally acquired cases of common cold.

In a personal communication Andrews[9] stated that using two similar strains of filtered nasal washings he was able to reproduce symptoms of minor respiratory disease in about 50 per cent of human volunteers. Filtration studies of these agents suggested a particle size similar to or smaller than that of the influenza viruses.

In December 1947, Topping and Atlas of the Common Cold Unit, National Institute of Health,[10] published a preliminary note describing the results of an attempt

to isolate, cultivate and identify the agent or agents of the common cold. Unfiltered nasal washings obtained from individuals within 24 hours of the onset of cold symptoms produced signs and symptoms of minor upper respiratory infection in five out of five volunteers in 36 to 48 hours. All five complained of fatigue, nasal obstruction, and frequent expectoration. Three complained also of sneezing, headaches, coughing, and burning, watery eyes. Two experienced prodromal chilly sensations and hot flashes. Objectively, hyperemic obstructed nasal passages, red throats with prominent lymphoid follicles, and large quantities of postnasal mucus for 2-5 days were evident. Slight temperature elevations between 99°and 99.6° developed after onset. One volunteer suffered all the above complaints to a more severe extent, and in addition developed moderate rhinitis, a mild laryngitis for a day, moderate pharyngitis, episodes of sharp, sticking pains substernally for 3 days (X-rays normal) and a temperature elevation to 102°F. for a day.

Nasal washings from the volunteer who developed the more severe clinical disease were inoculated into embryonated hen eggs and several substrains were obtained after varying numbers of allantoic passages. One of these substrains produced a mild illness similar to that in the original volunteer group. Another substrain produced 100 per cent illness of a more severe type in 14 volunteers.

Within 7-24 hours all patients in this group complained of dry, irritated throats (without objective pharyngitis) and exhibited malaise out of proportion to physical findings. Within a few hours nasal obstruction and postnasal discharge with frequent expectoration developed and remained prominent during the course. All complained of frequent supraorbital headaches, moderate sneezing, and an infrequent, mild, unproductive cough. Hoarseness was evident in 9, one of whom became aphonic for about 12 hours. Nine complained of burning, watering eyes (with mild conjunctivitis objectively) and vague chest aches without significant X-ray findings. Intervals of profuse serous rhinitis were observed in five. Early in the illness, five complained of chilly sensations and hot flashes. Objective signs of pharyngitis, lymphoid follicular prominence, hyperemic obstructed nasal passages, and profuse postnasal discharge were observed in all. Temperatures between 99°and 100°F. occurred at irregular intervals in 12 volunteers. No significant urine or white blood count changes were apparent.

Sixth- and seventh-passage allantoic fluids containing this substrain produced moderately severe illness in fifteen out of sixteen, and fourteen out of sixteen volunteers respectively.

In sum, sixty individuals in eight groups were inoculated with allantoic fluid containing this agent. Of the sixty, fifty-seven developed a characteristic syndrome reminiscent of the minor upper respiratory infection of the donor. Microscopic studies have failed to reveal bodies suggestive of bacteria or the larger viruses. On the other hand, preliminary electron microscopic examinations have shown characteristic particles of the same general size as viruses of the influenza type, but readily distinguishable from them.

A number of further studies are being made by the Common Cold Unit of the National Institute of Health. Among these are:

Attempts to determine by laboratory and human volunteer tests whether different disease entities are involved in the minor respiratory illness known as "the common cold."

Determinations regarding immunity that may be conferred by agents of minor respiratory illness.

Duration of infectious spread in humans of illness produced by these agents.

Physiological studies, including blood and urine chemistry balance during infection.

Quantitative nasal flora changes during periods of infection.

Differences in epidemiology of the disease according to mode of inoculation.

Reisolation of virus from volunteers infected with egg material.

Concentration of virus by various procedures which keep it alive so that particles of only one type can be visualized under the electron microscope.

In addition to the research of the Com-

mon Cold Unit of the National Institute of Health, the U. S. Public Health Service is supporting common cold research by other groups through its research grant program.

It is clear from evidence of past work that the common cold has been one of the most complex and difficult medical research problems. It is equally clear that here is a problem wherein substantial progress demands coördinated, concerted teamwork by patient and careful investigators representing many scientific disciplines. The biochemist and the biophysicist, the clinician and the epidemiologist are only some of those who must contribute their special skills.

The incentive for coördinated hard and patient work to solve the problem of the common cold is more than merely advancement of scientific and medical knowledge. The real challenge is found in the fact that the common cold is the most prevalent and the most highly infectious of all the communicable diseases. There is general agreement among investigators in this field that the average person suffers at least two colds in the course of a year, giving a total of approximately 300,000,000 colds annually for the general population of this nation. The duration of a simple cold averages about five days. Thus, multiplying the number of colds by their duration, one finds that the people of the United States each year suffer about 1,500,000,000 days of discomfort and reduced efficiency, if not of actual disability, from this cause.

Various studies indicate that from 40 to 50 per cent of all days lost from work are attributable to colds and their complications. It has been conservatively estimated that the toll of the common cold in this country is at least one working day per employee per annum. If that is so, there will be more than 60,000,000 days lost to industry this year because of colds. Even at an average daily wage of $7, the loss in wages totals more than $420,000,000.

The cost of drugs and medical care must also be added. Accurate statistics on this subject are not available, so that it is necessary to resort to speculative estimates. On the assumption that every family in the United States spends on an average of $10 a year for drugs and medical care in the treatment of colds, the total amount spent for these items would be in the neighborhood of $400,000,000.

The cost to employers resulting from lost production and disrupted routine is extremely difficult to estimate. It is certain, however, that the annual cost of colds to employers is very considerable for the country as a whole.

On the basis of the figures cited above, it is thus estimated that the cost of the common cold to the American people is well over a billion dollars a year. Although the common cold is generally considered a minor infection, any disease that runs to such astronomical figures in cost must be rated high in the list of enemies of the public health.*

* Source: Statistical Bulletin. Metropolitan Life Insurance Company, Vol. 28, No. 11, November 1947, pp. 6-7.

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The Relationship of Bacteria to the Common Cold

YALE KNEELAND, JR.

This subject is a complex and surprisingly vague one. Much of the available data are very old, and in the forthcoming discussion I shall lean heavily on work done many years ago by ourselves and others. To begin with, I am going to pose four questions, and the discussion will take the form of an attempt to answer them. The four questions are as follows:

1. What bacteria are important in common upper respiratory infection?
2. Can and do bacteria initiate colds?
3. If not, what role do they play in colds?
4. What relationship do they have to epidemiology?

Let us now attempt to frame answers to these in order:

1. β hemolytic streptococci, H. influenzae and pneumococci need no defense as respiratory pathogens, and I am going to assume that they are pathogenic. I assume that Friedländer's bacillus is also a pathogen, but it is sufficiently rare so that I am going to omit it from the discussion. Abundant studies of respiratory bacteriology for many years have indicated that various Neisseria, non-hemolytic streptococci, diphtheroids, etc. constitute the normal "basal flora," and are not significant in disease. I am going to add staphylococci to this basal flora, for although they may occasionally act as secondary invaders, I believe that this role has been considerably over-emphasized in the past, particularly by otologists. The discussion, therefore, will revolve around hemolytic streptococcus, H. influenzae, and the pneumococcus.

2. Can and do bacteria initiate colds? If we consider our three pathogenic organisms one by one, the idea of exudative pharyngitis due to hemolytic streptococcus immediately comes to mind. "Strep. throat," "follicular tonsillitis"—certainly this is a clinical entity of which the hemolytic streptococcus is commonly believed to be the cause. But can a virus component in the etiology be dismissed? It seems to me that it can be. For one thing, some of the most florid outbreaks of this condition have been shown to be milk- or food-borne. Moreover, the spread of hemolytic streptococci in hospitals, particularly from nasal carriers, was carefully studied in the last war, and there was no evidence of a virus component. It would appear, therefore, that the hemolytic streptococcus may be a primary incitant of common respiratory disease—but it causes "strep. throat," and this is *not* the common cold.

In regard to H. influenzae and the pneumococcus, no strictly analogous situation exists. To be sure, there have been rare outbreaks of disease such as the so-called "Woodside throat" in Australia at the beginning of the last war, which were believed due to a primary H. influenzae pharyngitis of very severe character. Cooke et al[1] adduced some evidence against a virus component here, but it was not conclusive. On the other hand, our own studies[2] as well as those of others, would indicate that when nose and throat cultures are taken in the same individuals regularly, both H. influenzae and pneumococci may appear and disappear in a manner apparently unrelated to attacks of the common cold. Even in the well-known studies of semi-isolated communities by Burky and Smillie,[3] where these organisms were prominent during epidemics respectively in Labrador and Alabama, they could not be recovered in every case, and appeared late in many of the cases. The classical study of the completely isolated community (Spitzbergen) was reported by Paul and Freese in 1933.[4] It will be remembered that from December 1 until the end of May, the period when this little community was ice-bound, only 19 colds occurred among 500 inhabitants. Moreover, during the last

3 months of the period there were only four, three being in the same individual. Yet H. influenzae and pneumococci (as well as hemolytic streptococci) were recovered from the population throughout these winter months—and with about the same frequency as they were found when colds suddenly became rampant following the arrival of the first boat in the Spring. This whole experience powerfully suggested that bacteria were not the inciting agents of the common cold, at least of the communicable type, and the presence of a virus was naturally inferred. In reviewing all the evidence over the years, one is led to the conclusion that, while there is no proof that bacteria cannot cause colds, ordinarily they do not.

3. What role do pathogenic bacteria play in the common cold? It is very tempting to say that they act as "secondary invaders," and let the matter rest there. Yet when one studies the available evidence, it is extraordinary how difficult it is to define their function as secondary invaders. Dingle and his co-workers,[5] for instance, after exhaustive studies of acute respiratory disease in the Army, came to certain beliefs in regard to the streptococcus. For one thing, they concluded that hemolytic streptococcus caused only about a quarter of the cases clinically designated as "exudative pharyngitis," and where it was not etiologically significant the mere presence of streptococci did not affect the course of the disease. On the other hand, Coburn[6] reported that mass sulfadiazine prophylaxis in the Navy resulted in a marked reduction in hospital admission rate. He stated that the morbidity rate for virus diseases remained unaffected, but the data suggest that the principal result of prophylaxis was the virtual elimination of frank streptococcus disease in a highly susceptible population.

The pneumococcus presents a somewhat different problem. Experiences in our own infants and chimpanzees[7,8] both of which are highly susceptible to severe colds, indicated that the presence of this organism appeared related to the severity of the common cold. The same finding was made by Burky and Smillie[9] amongst Alabama school children. Another method of approaching the problem is by the use of specific chemotherapy or antibiotics. Siegel,[9] working at Letchworth Village with retarded children as subjects, concluded that early sulfadiazine treatment of common respiratory disease reduced the duration of fever, general severity, and complications in a controlled series. Lapin[10] gave oral penicillin to 160 children for a year and found the days of fever reduced from 24 to 5, and the number of febrile respiratory infections from 5.6 to 1.8 per child as compared with the previous year. Minor coryza, however, continued. On the other hand, Rusk and Van Ravenswaay[11] working with military personnel, a less highly susceptible population, found that sulfadiazine treatment of common respiratory disease did not affect the duration of fever or the length of hospital stay.

The situation in regard to H. influenzae would appear to be analogous to that of the pneumococcus. Burky and Smillie[9] made very similar observations of its behavior in Labrador to that of the pneumococcus in Alabama. We have noted it in severe colds both in the infant and in the chimpanzee. If we attempt to sum up, then it would appear that the role of the streptococcus is equivocal in instances where it is not the primary incitant of disease, and that pneumococcus and H. influenzae can enhance the clinical severity of colds in highly susceptible individuals, and produce such complications as sinusitis, otitis, and pneumonia. On the other hand, most of the effects of the common cold in adults are probably due to the virus and not to bacteria.

4. Are bacteria related to epidemiology? Again, the evidence on this point is rather scanty, and tends to be indirect. We observed[12] in the chimpanzee a shift from the R to the S form of H. influenzae in throat cultures taken during spontaneous and experimental colds. In free intervals only the R form could be recovered, but with infection a reversion took place to the same S type as that obtained during the previous cold. This highly suggestive example of interaction of virus and bacterium has never

been duplicated in man. In another very susceptible type, however,—the human infant—we have noted some apparent relationship of the two types of agents. In a group studied throughout one winter[12] it was believed that the first Autumn wave of colds, presumably of virus origin, resulted in a widespread dissemination of pneumococci. Then, later on, when the carrier rate was 80 per cent or thereabouts, an outbreak of colds took place which showed not only considerably increased clinical severity, but also a higher incidence. It is also worthy of note that in Burky and Smillie's experience[3] the outbreak of colds in Alabama and Labrador—again in very susceptible populations — associated with pneumococcus and H. influenzae, also showed this clinical severity and high incidence.

With such evidence as this before us, it is permissible to frame a tentative answer to the last question. One action of the virus may be to increase the dissemination of pathogenic bacteria, and perhaps in certain instances to alter their essential virulence. With the ground thus prepared, the same or another viral agent, acting in conjunction with bacterial agents, may be more highly communicable and more infective.

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